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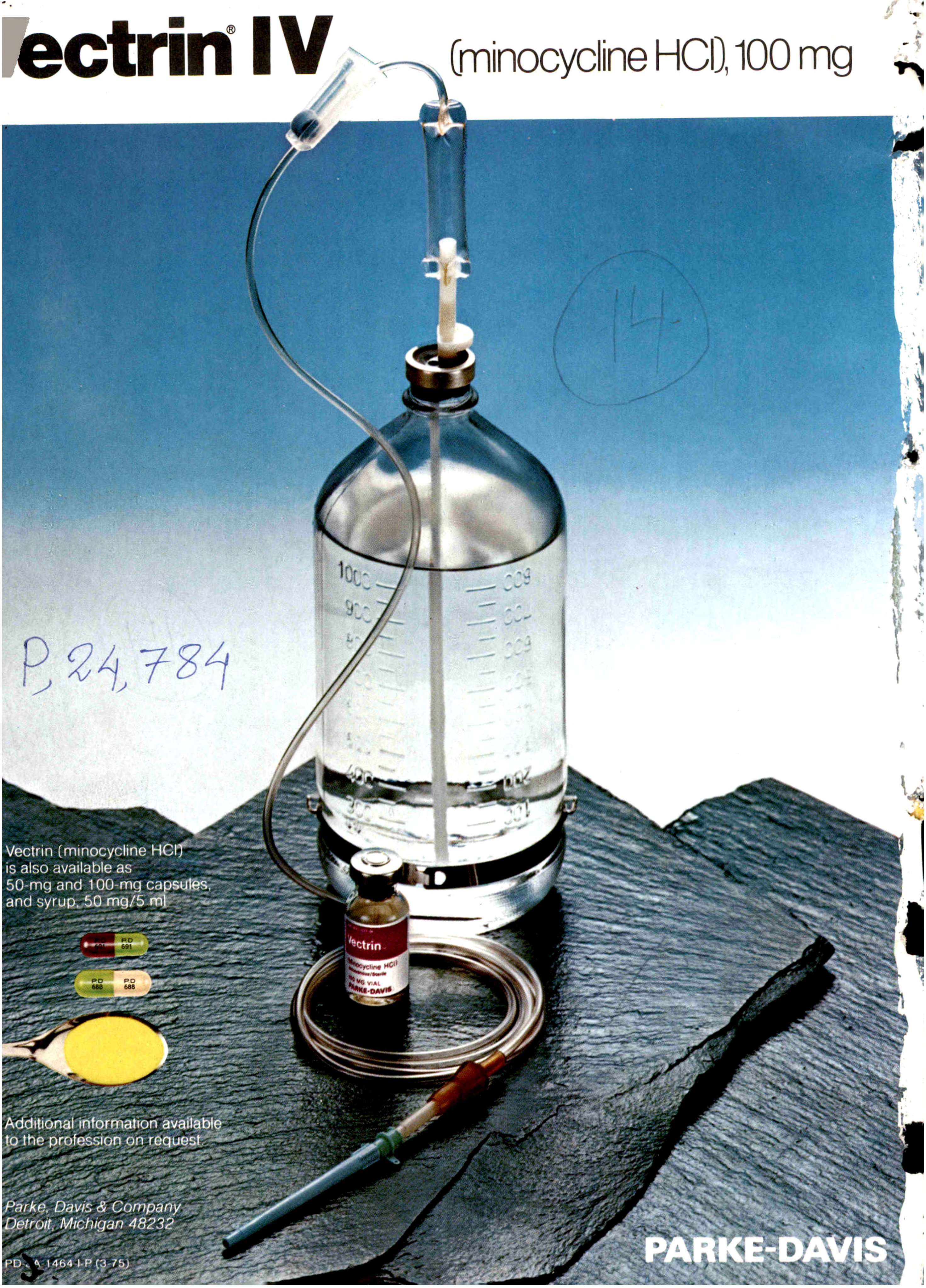

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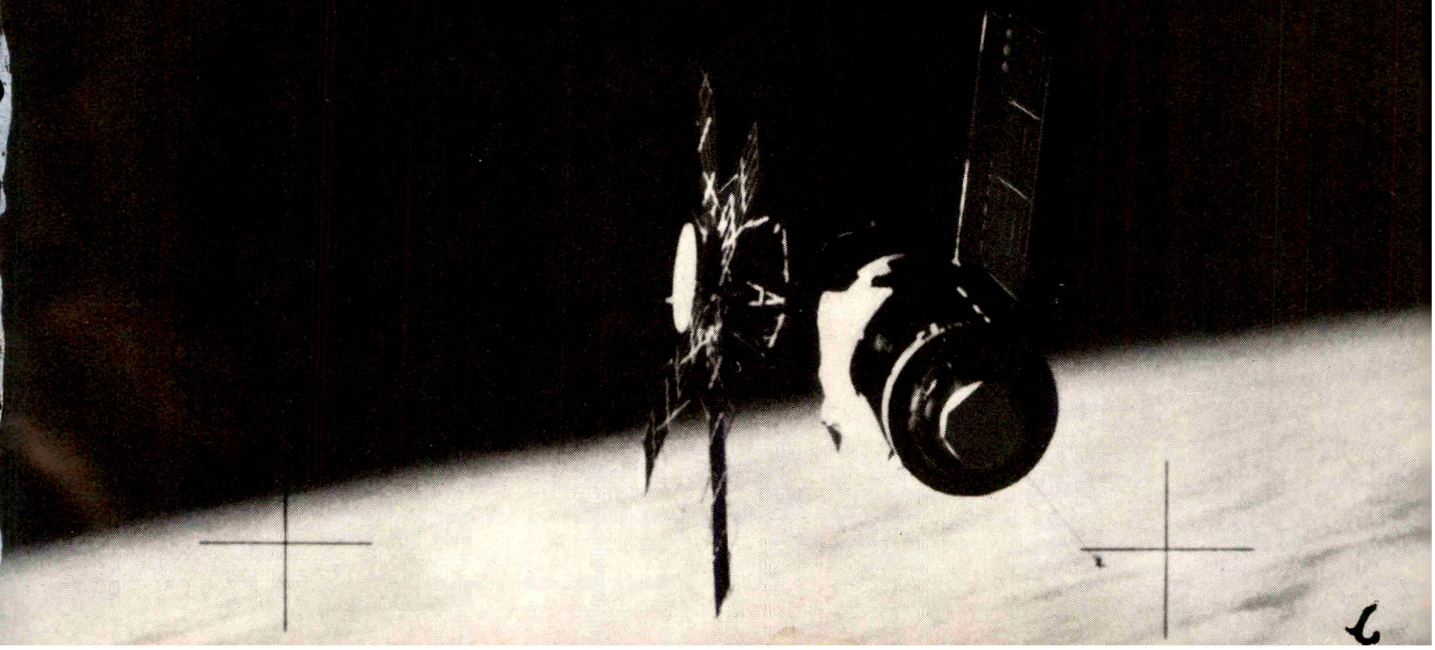

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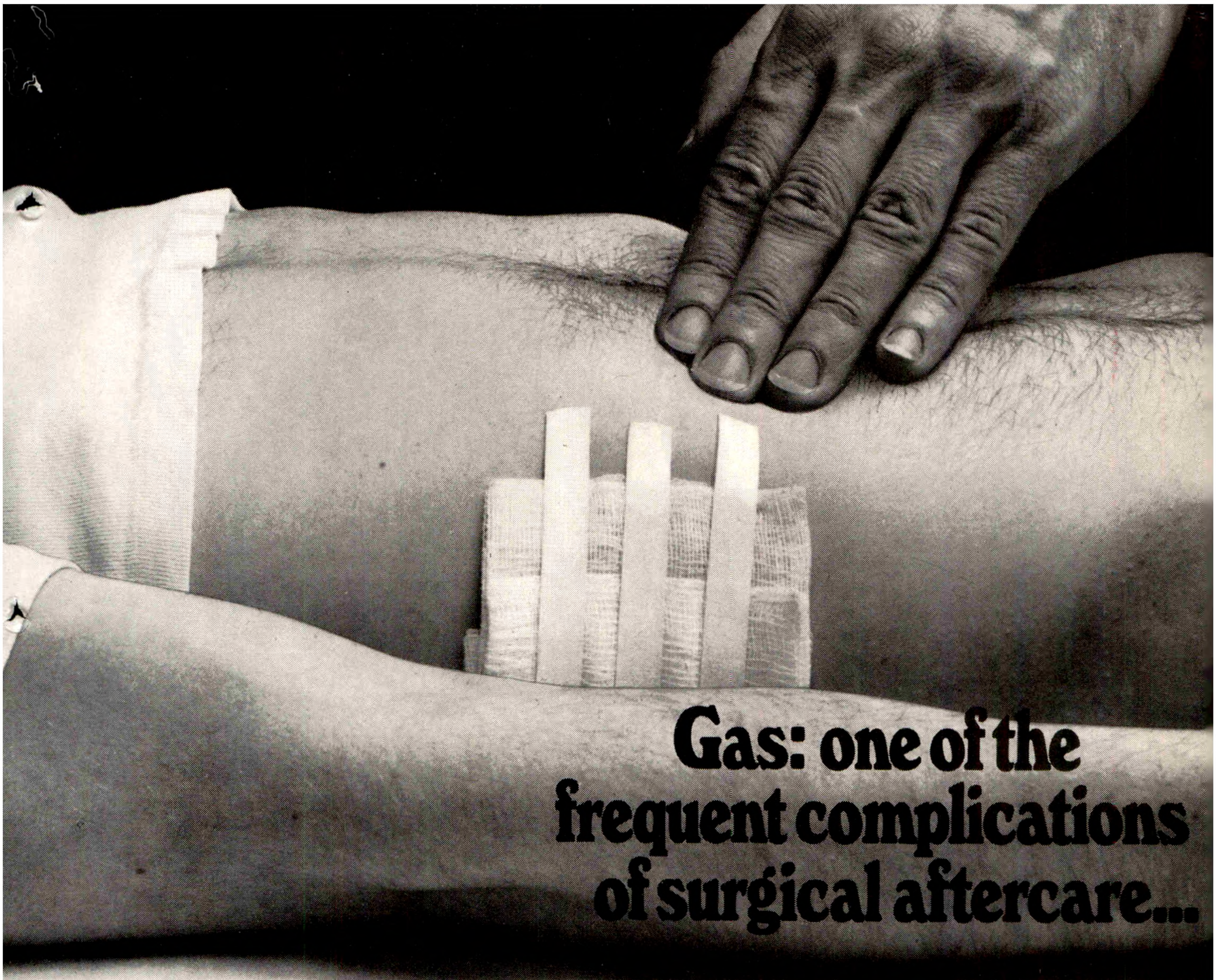

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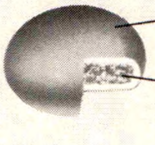

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol. 38*:386, Sept. 1971.
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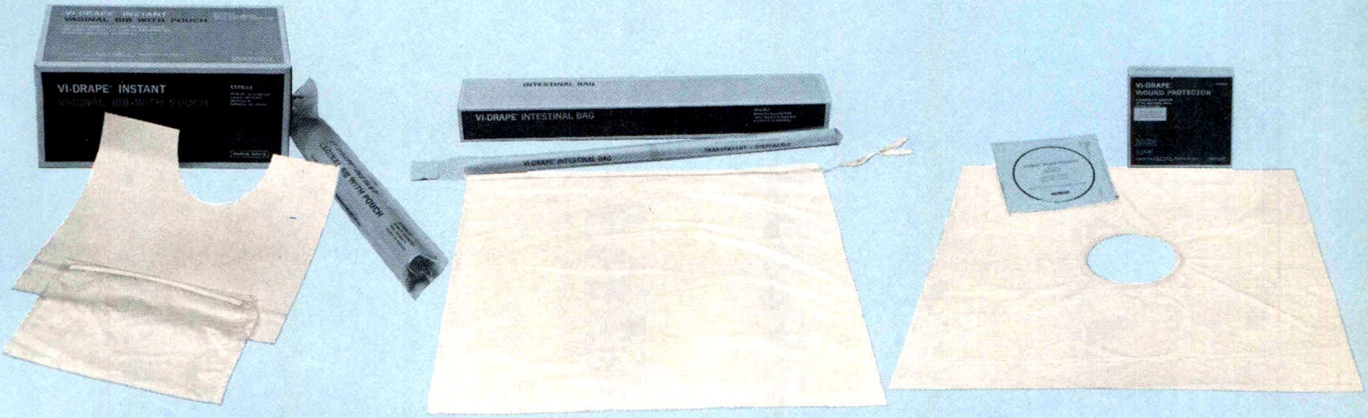

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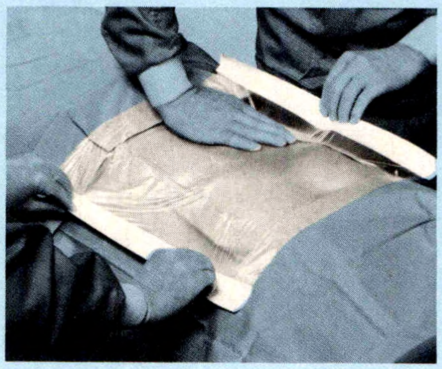

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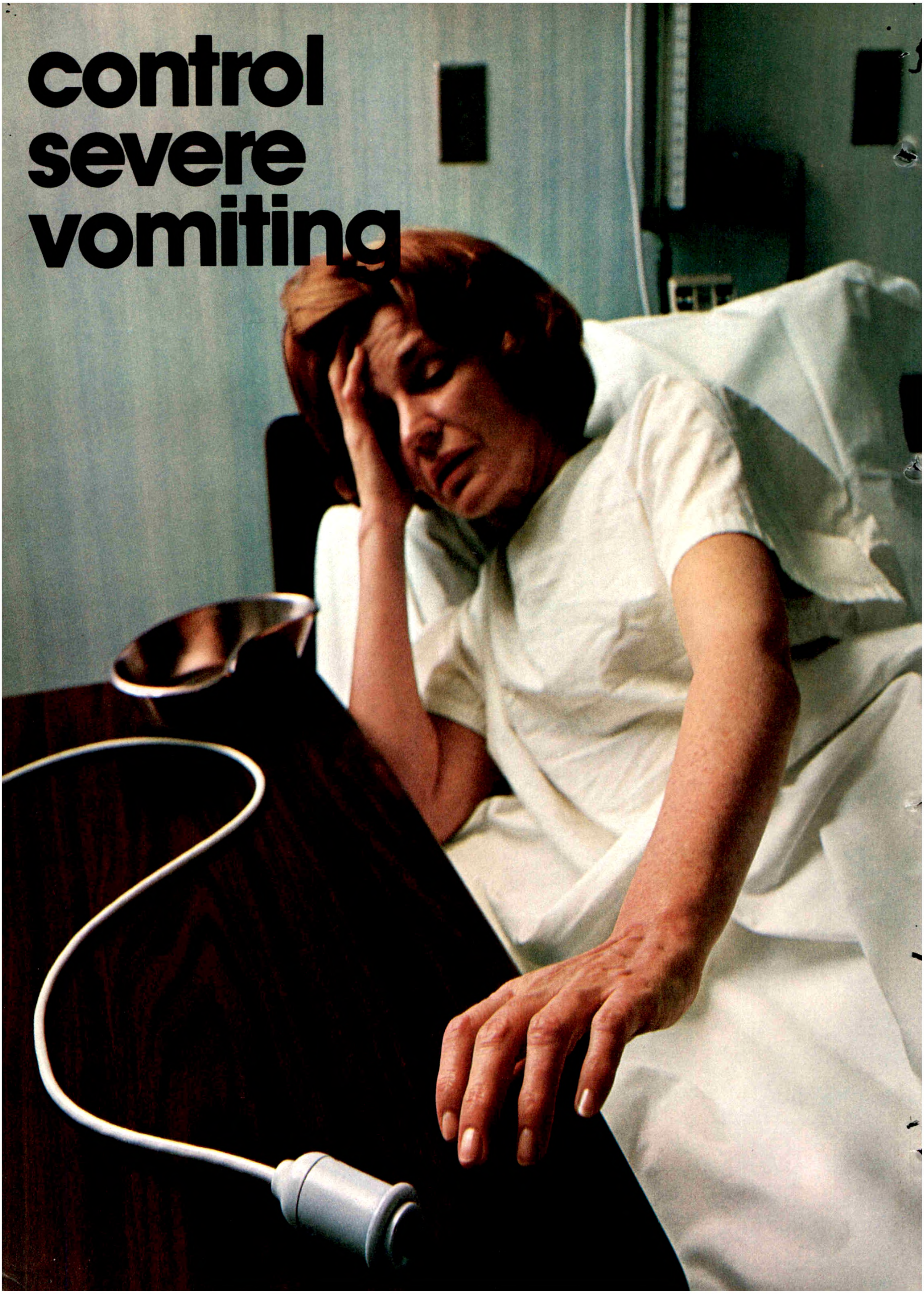
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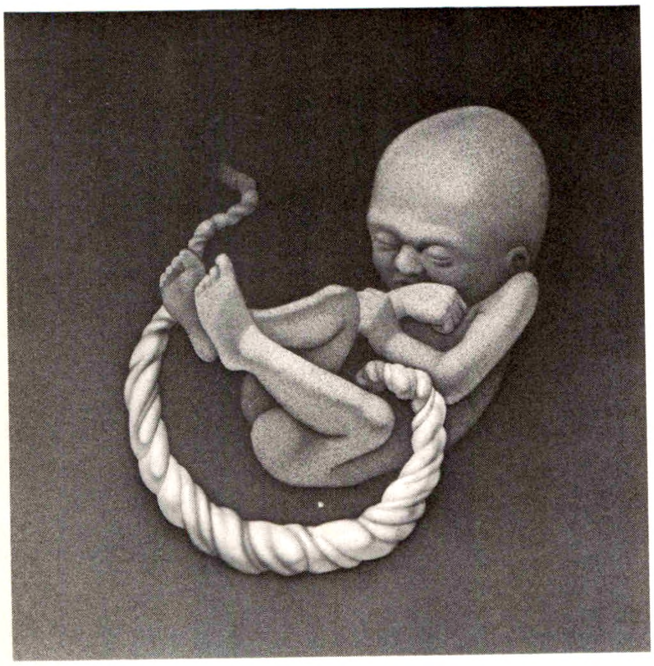

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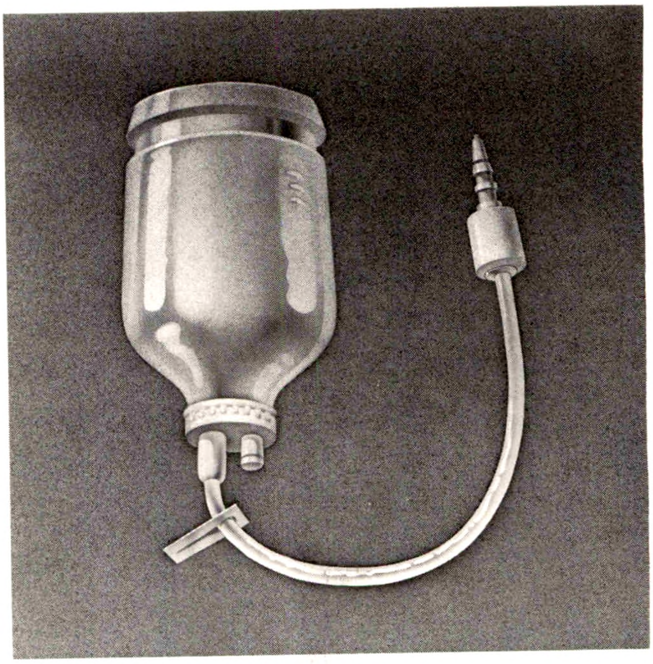

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Selection of Patients and Operative Approach in Primary Aldosteronism

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A system for discriminating between adrenal adenoma and hyperplasia based on the levels of aldosterone production, plasma renin concentration, severity of electrolyte disturbances, plasma aldosterone patterns during recumbency and after assuming erect posture, and ^{131}I-19-iodocholesterol scan has been developed. Indicated for operation are patients with adenomas whose elevated blood pressure cannot be continuously controlled with usual doses of medication and patients with documented deterioration of target organ function. Adrenalectomy has been performed 83 times in 81 patients with a diagnosis of primary hyperaldosteronism. Results of excision of adrenal adenomas have been excellent with significant lowering of blood pressure in all cases and cure of hypertension in over 60%. Results of total or subtotal adrenalectomy for hyperplasia have been poor with almost all patients still requiring medication for hypertension. Adenomas have always been unilateral, and usually can be localized so that unilateral exploration is curative. Therefore, we have tried to distinguish preoperatively between adenoma and hyperplasia. Anterior transperitoneal adrenalectomy has been effective with few complications, and no postoperative hypocortisolism after unilateral adrenalectomy for adenoma. The unilateral extraperitoneal approach gives shorter morbidity and potentially fewer serious complications.

ALTHOUGH PRIMARY ALDOSTERONISM is a relatively rare disease, it is a significant cause of correctable hypertension, and therefore must be considered in the care of every patient treated for high blood pressure. Unfortunately, this disease takes many forms and only in primary aldosteronism due to adenoma, is surgical therapy truly effective in eliminating most or all manifestations of the disease. Therefore, after primary aldosteronism is diagnosed, a number of decisions remain before operation can be elected, and some decisions may remain to be made during the operative procedure.

We have studied over 115 patients with primary aldosteronism and have performed 83 operations on 81 patients during a 14-year period. The first 24 patients were previously reported to this Society by Silen and Associates in 1966.[13] Based on this experience we have formulated a system of categorization in which selection of patients for adrenalectomy is an important part.

For analytical purposes, we have categorized primary aldosteronism into five major categories: 1) Aldosterone-producing adenoma (APA); 2) Idiopathic aldosteronism due to bilateral adrenal hyperplasia (IHA); 3) Adrenocortical cancer; 4) Glucocorticoid-remediable aldosteronism, and 5) "interdeterminate aldosteronism," a group of patients whose signs, symptoms, and biochemical findings do not conform to any known category. Adrenal surgery has not been performed in these pa-

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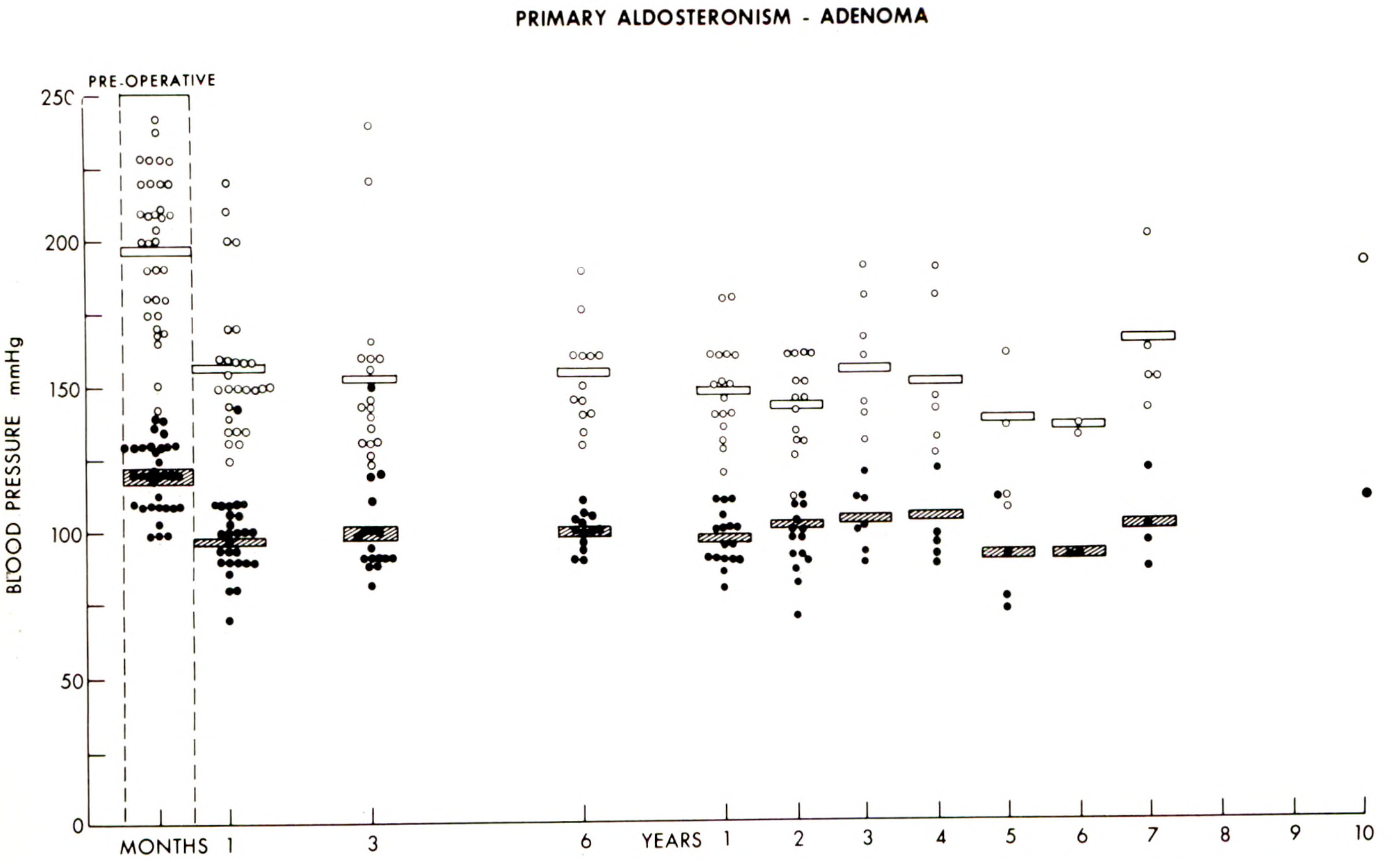

FIG. 1. Blood pressure response in patients followed for long periods after total or subtotal adrenalectomy for bilateral adrenal hyperplasia.

tients. Therefore, pathologic diagnosis is not available.

Extirpation of an APA will completely control the metabolic manifestations of aldosteronism, hypervolemia, potassium wasting, alkalosis, weakness, fatigue, and loss of sympathetic vasoactive reflexes. Hypertension is completely controlled in about 60% of patients and improved in the remaining 40% (Fig. 1).[4]

Unfortunately, patients who have had adrenal hyperplasia (IHA) have not responded well to adrenalectomy (Fig. 2). Control of the metabolic manifestations has often been achieved, but hypertension is rarely cured, and recurrence or persistence of metabolic alkalosis, sodium retention, and hypokalemia is frequent unless all or almost all adrenal tissue is removed. Therefore, we feel that it is not usually advisable to operate on patients with this form of the disease since operation, even total adrenalectomy, seldom offers a better quality of life than does medical therapy alone.[4,7]

Adrenocortical cancer manifesting itself as aldosteronism is rare and seldom surgically cured. It, too, has a wide spectrum of effects. We have experience with two such patients, and, fortunately, both are alive and essentially well at 2 and 9 years.

Treatment with cortisol completely cures the rare patient who has the glucocorticoid-sensitive form, and such patients never need operation.

Diagnosis and Categorization

The patient is diagnosed as having either primary or secondary aldosteronism by a series of tests including serum electrolyte concentration, urinary electrolyte excretion, urinary aldosterone excretion, plasma aldosterone concentration, plasma renin activity, and renal function tests. Chronic diuretic therapy and chronic licorice ingestion can mimic primary aldosteronism and must be avoided during this and subsequent phases of the investigation. A useful screening test is the measurement of serum and urinary potassium done while the patient has a normal or high sodium intake. This diet provokes hypokalemia in patients with primary aldosteronism. On rare occasions, aldosterone may have to be measured while the patient's serum postassium is relatively normal since potassium depletion can retard aldosterone production. If aldosterone concentration and excretion are elevated, 17 hydroxycorticosteroids are normal, plasma renin concentration is suppressed, potassium wasting is proved, and renal function is not severely impaired, primary aldosteronism is diagnosed.[2]

At this stage, the differentiation between IHA and APA can already be made with some accuracy. Quadric analysis of multiple variables[1] including aldosterone excretion level, serum potassium, plasma renin, hyper-

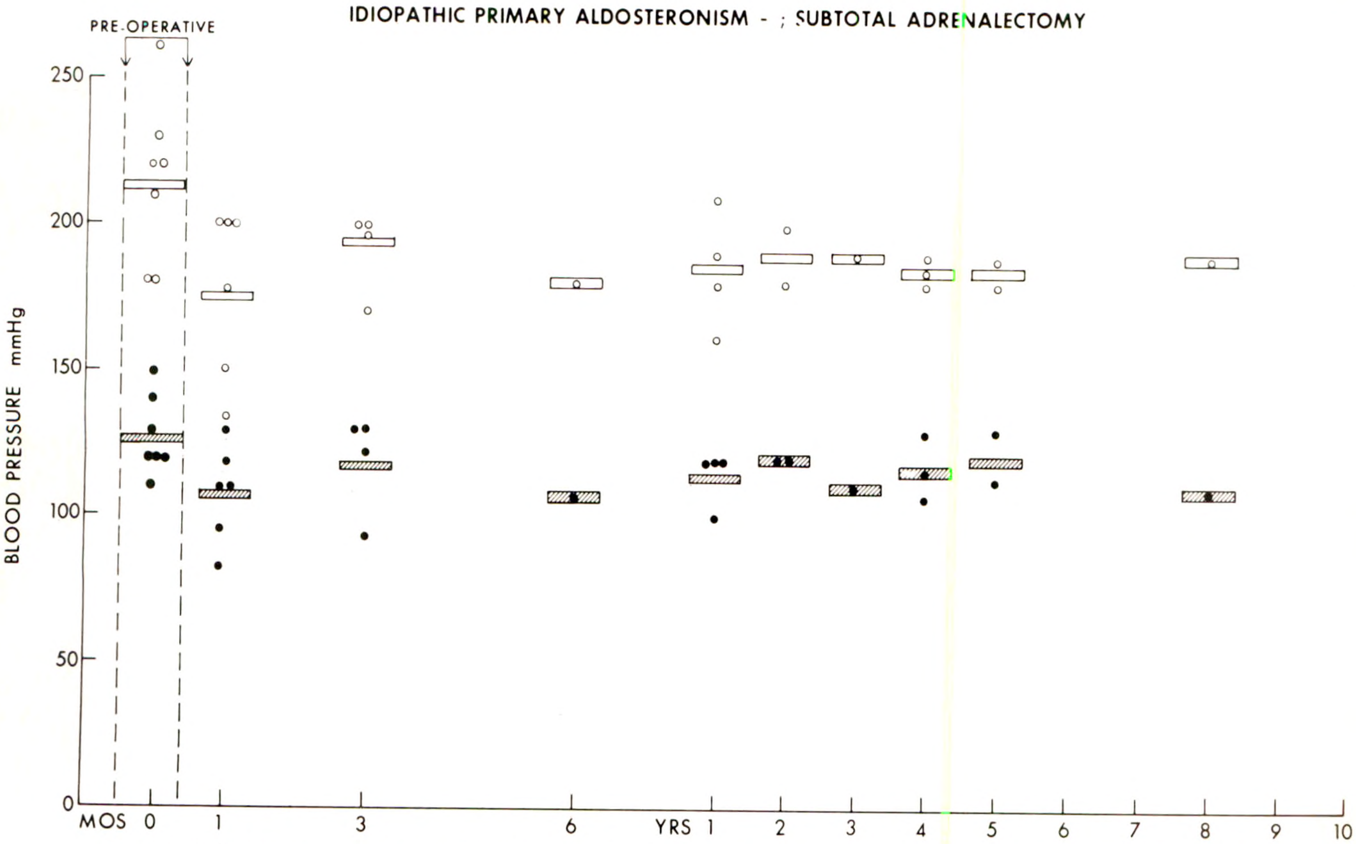

FIG. 2. Blood pressure response in patients after unilateral adrenalectomy for aldosterone-producing adenoma.

tension, age, and sex can be mathematically analyzed, and, in most cases, this analysis can distinguish between the two forms. Other forms of discriminants, such as linear discriminant analysis based on plasma renin concentration plotted against aldosterone excretion after DOCA treatment can be used.[3,5] In general, the more complete the syndrome, the more likely the patient is to have an APA.

Since none of the analyses of the total syndrome provide an exact differentiation between APA and IHA, we have sought more direct evidence to distinguish between the various forms. The introduction of tests based on diurnal variations of aldosterone production, and adrenal scanning with ^{131}I-19-iodocholesterol seem to have provided such evidence.[3,9]

In normal, recumbent patient the diurnal variation of aldosterone parallels that of cortisol, reaching a low in the evening and a high in the early morning. When the normal patient assumes the erect posture in the morning, however, plasma renin rises, followed by increased plasma aldosterone concentration. Aldosterone production in the patient with IHA is presumably still under the influence of renin since patients with IHA have normal diurnal variation during a 24-hour recumbent period, but their aldosterone level rises on standing. On the other hand, an APA has presumably become more autonomous, no longer responds to postural changes, but still follows the ACTH circadian rhythm. Patients with APA, therefore, have normal diurnal variation of plasma aldosterone while recumbent, but during standing the recumbent type of diurnal variation continues, and plasma aldosterone parallels cortisol concentration. As a result of these findings, plasma aldosterone concentration was measured after overnight recumbency and after 4 hours in upright posture in the 30 patients (Fig. 3). In the group of patients with APA whose aldosterone rose on standing, two of the "changes" were within the limits of error of the method, and two others (the largest changes) paralleled paradoxical changes of cortisol and thus were indeterminate tests. This test, therefore, is a most promising discriminator.[3]

Patients who have had adrenal carcinoma manifesting as hyperaldosteronism have had extremely high aldosterone secretion. One patient also had elevated cortisol and compound S. The other patient secretes only aldosterone at extremely high levels. Plasma aldosterone concentrations throughout the day are chaotic and without pattern in adrenocortical cancer.

If the patient has a well developed primary aldosteronism syndrome, and responds to the erect posture with a fall in plasma aldosterone, an APA can be diagnosed with high accuracy. In our patients, APA has al-

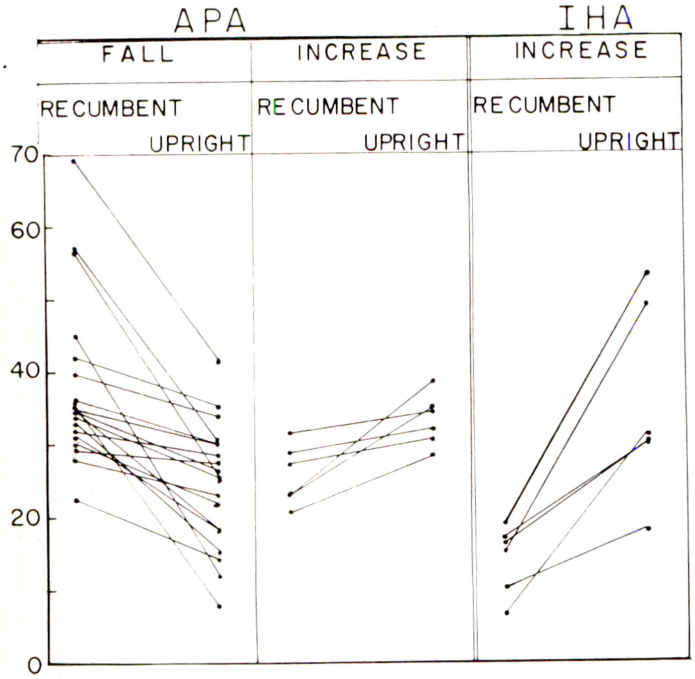

FIG. 3. Changes in plasma aldosterone during sustained erect posture after baseline early morning plasma aldosterone. See text for explanation of apparently anomalous results in center column. The two larger rises in APA cases both paralleled paradoxical elevations in cortisol and were thus nondeterminant.

ways been unilateral. Therefore, the next step is to localize the adenoma by performing a ^{131}I-19-iodocholesterol scan. This test has two functions: if the adenoma clearly localizes, not only is the diagnosis of adenoma confirmed, but the side for a unilateral operation is determined.[8]

Isotope studies have been performed on outpatients at the Donner Laboratory of the University of California in Berkley. Serial scintiphotographs of the adrenal area were obtained between the third and nineteenth days after injection (Fig. 4).

Thirty-one patients with suspected primary hyperaldosteronism were studied. Tracer lateralization was achieved in 10 patients, 8 of whom have been proved by operation to have adenoma on the predicted side. The two remaining patients have not yet had adrenalectomy. One patient who had equal, bilateral concentration of the isotope proved to have IHA. In the remaining patients (except the two with malignant disease) there was no lateralization, and no operation has been undertaken. The smallest adenoma diagnosed was 0.9 cm in diameter and became apparent only by computer analysis when scanning was continued through the nineteenth day. Smaller adenomas, therefore, may be difficult to localize.

Two patients, who were already thought to have carcinoma, had more difficult scans to interpret. One patient, whose tumor produced solely aldosterone, concentrated isotope on one side only and proved to have adrenal carcinoma on the side showing no function. The other patient, who secreted cortisol, compound S, and aldosterone, had an atrophic gland on the other side and visualized neither gland on scan. Both patients were explored through the abdomen and both sides were inspected for verification of diagnosis.

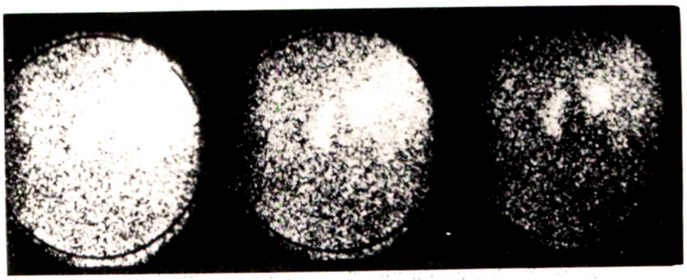

FIG. 4. ^{131}I-19-iodocholesteral scan showing adenoma in the right adrenal.

Adrenal venous catheterization with measurement of plasma aldosterone and cortisol is sometimes helpful. This technique has not usually been effective in our hands, because we are only infrequently able to catheterize both adrenal veins. If an APA is present, cortisol will be synthesized by both glands, and adrenal venous effluent cortisol concentration will be about the same on both sides. A step-up of three times the systemic aldosterone on one side localizes the APA. If only one vein can be catheterized, and the diagnosis of adenoma is not secure, a "step-up" on the one side catheterized can be misleading because it is consistent with aldosterone production from a hyperplastic adrenal gland. Our single operation in recent years for hyperplasia was occasioned by undue reliance on a catheterization of only one adrenal vein and insufficient reliance on a non-lateralizing adrenal scan. In this case, a recumbent-erect, diurnal variation study was, unfortunately, not done.

During adrenal venous catheterization, venography can be done in the hope of outlining an adenoma. Unfortunately, adrenal veins are easily ruptured, and destruction of normal adrenals has been reported.[6] We find this technique unduly complex and dangerous and have not performed it since iodocholesterol scanning has become possible.

Patients placed in the indeterminate group undergo periodic testing and medical therapy until they clearly fall into a determinate group. This risks an occasional complication of hypertension, but tends to reduce the risk of ineffective operation on adrenal hyperplasia. These patients as a group have responded well to spironolactone therapy, and operation has rarely been elected.

Indications for Operation

Adrenalectomy is not always required even when APA is unequivocally diagnosed. During the testing program, most patients have been given spironolactone. If a dose of less than 150 mg/day completely controls hypertension, the metabolic syndrome, and the symptoms of fatigue, carpopedal spasms, and nocturia, adrenalectomy is not usually elected since side effects of spironolactone are rare at this dose level. Severe side effects may preclude this form of treatment. The response to spironolactone rather accurately has predicted the response to adrenalectomy for APA. Patients electing nonoperative management must be periodically re-evaluated. Any change in target organ function or difficulties in controlling blood pressure indicates adrenalectomy. Patients who obviously present a surgical risk are held longer on medical management. Young patients are encouraged to have the operation early.

An occasional patient from the interdeterminate or the IHA groups may be selected for operation because of the severity of his or her disease. We have undertaken such operations reluctantly, but despite the lack of effect on blood pressure, some patients have noted relief of hypokalemia and significant decrease in fatigue which is the paramount symptom of significant hyperaldosteronism.

Preoperative Preparation

The major objective of preoperative preparation is to have the patient normokalemic during operation. Most of our patients have been treated with antihypertensives up to several weeks before operation. However, if the patient has been severely hypertensive, we have continued alpha methyl DOPA up to the day of operation. Patients who are hypokalemic are admitted several days in advance and are treated with sodium restriction (up to 20 mEq/day) and potassium repletion up to 6-8 gm KCL/day in addition to diet. A positive potassium balance is achieved, but it is seldom possible or necessary to replete the total body potassium deficit.

More recently, patients have been treated up to the time of operation with spironolactone. In 10 such patients, we have found this an acceptable, sometimes preferable, alternative. It is important to understand, however, that the patients' postoperative needs have varied significantly according to the preoperative preparation (see /Postoperative Care).

Operative Approach

During the first years of our experience, we almost routinely approached the adrenals transperitoneally through an anterior bilateral subcostal incision. The left gland was approached using the "transligamentous" dissection in which the gastrocolic ligament is divided and the pancreas is mobilized anteriorly and superiorly by incising the posterior peritoneum at its inferior edge. This leads the dissection to the anterior surface of the left adrenal and tends to prevent damage to the spleen and splenic vein. Both adrenals were routinely exposed, and the diagnosis of IHA or APA made on inspection of both adrenals. With some experience, this is surprisingly easy to do. In fact, it is often easy to determine which gland contains an APA even before the adenoma can be seen or felt since in our experience, half of the glands containing an adenoma are also visibly hyperplastic while the contralateral gland is normal (see Pathology).

Before the decision is made to remove adrenal tissue, both glands must be inspected carefully. The anterior and posterior surfaces should be freed of surrounding tissue, from the upper to the lower pole, and the medial surfaces partially freed. We have routinely practiced this extensive exposure; yet, we have had no remaining single adrenal gland fail to function adequately. The dissection is done with use of fine metal clips and electrocautery. The adrenal gland must never be grasped with instruments. If it is, a medullary hematoma will develop and confuse the identification of adenomas. If a hematoma does confuse the evaluation, it can be evacuated safely by piercing the cortex with a knife.

Three patients were surgically re-explored because previous surgeons at adrenal exploration failed to recognize the pathology. One patient had bilateral hyperplasia and two had undiscovered adenomas in the upper pole of the right gland, the most difficult area of adrenal gland to expose.

Despite the apparent magnitude of the transperitoneal procedure, it has been extremely safe in our hands. Operative complications are listed in Table 1. There has been only one death in this series. This occurred in the early 1960's in one of the first patients to be operated upon and death was the consequence of postoperative bleeding at a renal biopsy site. Renal biopsies are no longer done except on special indication, and the succeeding 80 patients have been operated upon without mortality.

Since 1965, every operation has been done or super-

TABLE 1. *Operative Complications of 59 Operations Done Since 1965*

	Anterior transabdominal (42)	Posterior or flank (17)
Venous injuries	2	0
Pancreatitis	0	0
Splenic Injury	1	0
Liver Injuries	0	0
Wound Infection	1	0
Wound Hematoma	1	2
Pneumothorax	0	0
Atelectasis-minor	Frequent	Frequent
Atelectasis-lobar	0	0
Pneumonia	0	0
Pulmonary Embolism	0	?1
Hernia	0	0

P, 24,784

vised by one of the authors (T.K.H.) and complications are shown in Table 1.

Both venous injuries incurred in the anterior approach were caused by too vigorous retraction of tissues. One was avulsion of the inferior mesenteric vein from the splenic vein and one a partial tear of the right venal vein from the vena cava. Both were easily repaired.

The postoperative course was medically complicated by significant cardiac arrhythmias in two patients (one of whom had transient severe hypertension and oliguria) who had severe hypertensive cardiovascular disease preoperatively, and had relatively low K^+ at operation. Early in our experience, when we overestimated intraoperative fluid needs, bladder catheterization was often necessary. Now that fluid replacement is kept below about 1 liter, catheterization is rarely necessary.

In the last few years, localization of the APA has been accurate enough to allow the use of a unilateral posterior approach in many patients. Our method has been essentially that of Young.[10] In this approach, the 12th rib is resected after the paraspinous muscles are retracted medially, and the pleural reflection is identified by having the anesthesiologist give a large inspiration. The insertion of the diaphragm to the periosteum of the rib is identified and detached. The pleural space is occasionally entered, but the hole is easily sutured at the end of the operation with a small suction catheter in place. The catheter is then removed. No pneumothoraces requiring further treatment have resulted. Gerota's fascia is then incised and the adrenal gland is identified. A hip rest which allows the abdominal wall to fall freely downward is extremely helpful both to the surgeon and the anesthesiologist.

The posterior approach is better tolerated by the patient, as three patients who have had both types of operations have testified. Patients, in general, have eaten and ambulated freely about 2 days earlier after unilateral posterior operation.

One patient who was 6 feet 5 inches tall, and weighed over 300 pounds, was operated upon by a flank approach for removal of a right-sided adenoma.

Postoperative Care

It is rarely necessary to give blood during either operative approach. Only 5 patients received blood. A total of 8 units were given. Three were used in a bilateral re-exploration. The average intraoperative fluid need is about 1 liter which is usually given as Ringer's solution.

Fluid needs after operation vary with the type of preoperative preparation. If the patient has been prepared without antihypertensives and with sodium restriction and potassium repletion, he is given 5% dextrose and water at an average of 2500 cc/day. No saline or potassium is given unless it is specifically indicated by clinical signs of poor perfusion, hypotension, excessive weight loss, or excessive postural hypotension. Patients prepared up to operation with spironolactone often required saline intraoperatively and postoperatively. This is rational since the spironolactone has reduced the hypervolemia of untreated aldosteronism, especially when an APA is the cause.[11]

No cortisol is given unless the patient has had a total or subtotal adrenalectomy. Bilateral adrenal exploration with the removal of one adrenal with an APA has not once required the use of cortisol in our practice. One patient with adrenal cancer producing excesses of both aldosterone and cortisol required cortisol postoperatively until the remaining, visibly atrophic, adrenal recovered its function.

Antihypertensives are rarely required postoperatively and are not routinely continued. Most patients with APA show a definite lowering of blood pressure within a week of operation, but the full effect of adrenalectomy is often not complete for several months (Fig. 1).

We have measured aldosterone postoperatively in most cases.[4] It usually falls almost to zero when an APA is removed. About 10% of patients who have a very low aldosterone postoperatively will continue to lose weight. If the serum K^+ rises to above normal range, and if postural hypertension and continued weight loss develop, sodium chloride is added to the diet, since the hypovolemia does not usually become troublesome until after the patient is eating. If the added salt is sufficient to reverse this syndrome, fludrocortisone is given. Nine patients transiently have required postoperative fludrocortisone support for a few weeks, but four patients who had a very long history of hypertension still require it years later.

Pathology and Choice of Operation

Sixty-two of the 81 patients had unilateral adenomas. Eleven patients had bilateral hyperplasia without a dominant adenoma. Current controversies exist in other fields of endocrine surgery about the vague distinctions between hyperplasia and adenoma. There are analogous features in hyperaldosteronism. Four patients had bilateral hyperplasia with an obvious encapsulated adenoma in one gland. Twenty-one of 43 patients with dominant unilateral adenomas operated upon since 1965 have had clear evidence of hyperplasia as well as adenomas in the involved gland. Biopsies as well as inspection of the contralateral gland in 5 of these cases showed no visible or microscopic evidence of hyperplasia. The significance of this relationship between hyperplasia and adenoma in the same gland is unknown. This relationship probably accounts for a number of case reports of multiple adenomas in the same gland since hyperplasia often takes the form of multiple small nodules. The confusion atten-

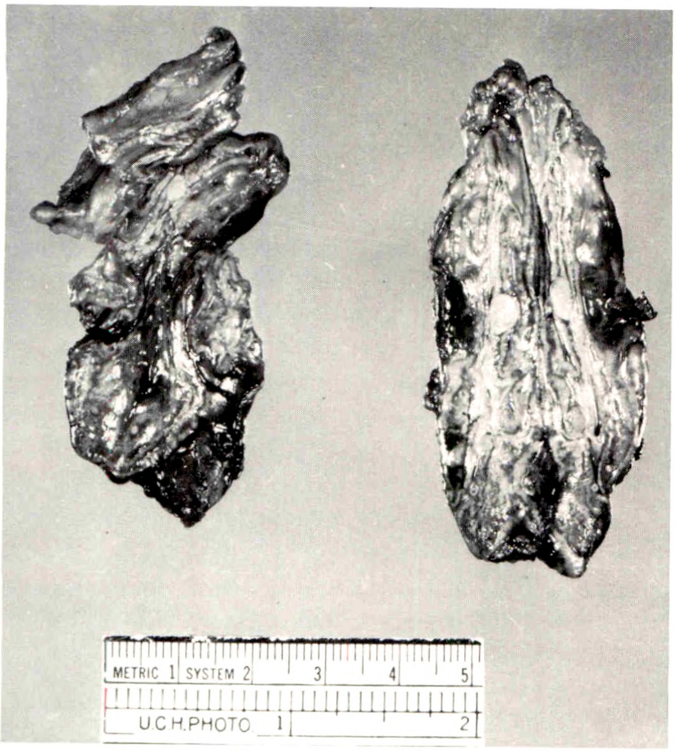

FIG. 5. Adrenal with florid hyperplasia. The other adrenal in this patient was similarly involved.

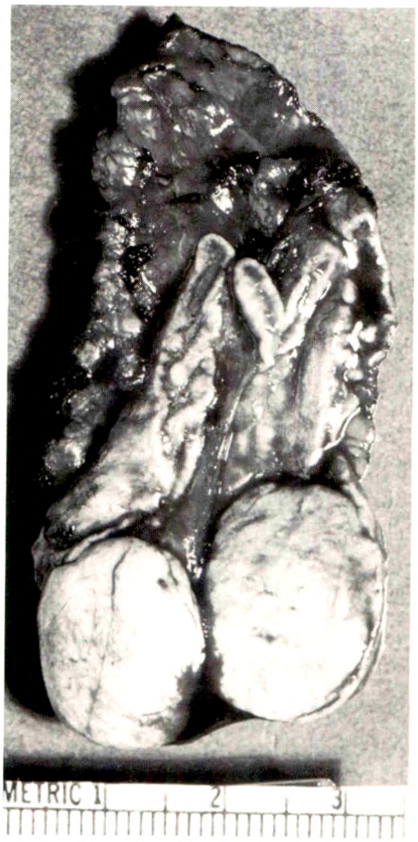

FIG. 6. Adrenal adenoma. Note the hyperplastic nodulation of the remainder of the gland.

dent upon the diagnosis of hyperplasia may also account for some cases of bilateral adenomas since hyperplastic nodules can brow as large as 5 mm (Figs. 5 and 6).

Because hyperplasia and adenoma often coexist, we would caution against partial adrenalectomy to remove adenomas since this may leave hyperplastic adrenal tissue in place. However, whether such tissue would actually have functional significance is unknown.

These observations also call into question the practice of unilateral adrenal exploration. Preoperative diagnosis is now so accurate that we expect to find pathology in every unilateral exploration, but there is then no way to visually assess the other gland. Retrospective analysis of unilateral adrenalectomy done for bilateral hyperplasia (4 patients) shows clearly that unilateral adrenalectomy is not as good therapy for IHA as is subtotal (80%) or total adrenalectomy (10 patients). However, only a few patients have been so treated. Four of our patients have had bilateral hyperplasia with adrenal adenoma on one side. Unilateral exploration therefore poses a risk that a hyperplastic adrenal may be left behind. This is not necessarily, however, a severe problem since the chance of curing such a patient, even with total adrenalectomy, is relatively small, and a second operation can be elected if further study shows continued disease and further target organ deterioration occurs. When an adrenal remnant is preserved, it is far preferable to have the remnant on the left since reoperations on the right gland are hazardous because the remnant adheres to the vena cava.

The total evidence suggests that posterior unilateral exploration is the procedure of choice for a patient who has a high probability of unilateral adenoma based on the various discriminants between APA and IHA and with unequivocal localization with iodocholesterol scan and/or complete bilateral adrenal vein catheterization data. When doubt exists, the bilateral approach, while a larger operation, is safe and potentially more effective.

The left adrenal is involved in 60% of patients, and women continue to outnumber men with primary aldosteronism (3 to 2). There continues to be no association between the size of the adenoma and the severity of the disease. There seems to be no relation between this disease and the multiple endocrine disorders. One patient, after adrenalectomy, was found to have a parathyroid adenoma. No other patients with multiple endocrine adenomas have been found.

The two patients with adrenocortical cancer were correctly diagnosed preoperatively. One patient, a 32-year-old woman with a large (15 cm in diameter) malignancy which secreted aldosterone, cortisol, and compound S has, by previous experience of others, a poor prognosis. Nevertheless, she remains well at 2 years on no medical therapy. The other patient, a 58-year-old woman, has an aldosterone-secreting tumor of low malignant potential which has been present for 9 years. Her extremely high aldosterone excretion halved when we removed about half of her widely scattered tumor nodules. Her symptoms are now relatively well controlled on spironolactone.

Two patients had apparently normal adrenals removed. One was operated upon early in the series when assay techniques were not as accurate as they are now. The other was operated upon a year before plasma renin activity assay became available. Retesting of this patient when the assay became available showed an extremely high plasma renin and a renin-secreting tumor was localized in the right kidney and removed with cure of his hypertension.[12]

Discussion

There is, as yet, no explanation of why adrenal hyperplasia behaves differently than adenoma or whether the two forms of the disease are even causally related. Unfortunately, the diurnal variation and postural tests have not been done on any of the 4 patients who had both adenoma and hyperplasia. We assume that these patients basically are suffering from bilateral hyperplasia.

The accumulated evidence of most reported series indicates that efforts to discriminate among the types of hyperaldosterone continue to improve the efficacy of adrenalectomy. Nevertheless, the safety of operative procedures in experienced hands contraindicates excessive efforts to avoid operation.

There seems relatively little difference in safety between the anterior, lateral, and posterior operative approaches. Each has its indications. The anterior approach in which both glands can be seen easily is particularly helpful in patients with suspected IHA, indeterminate primary aldosteronism, and patients with cancer. The surgeon who deals with this disease should be familiar with all three approaches to the adrenals. This is especially important when reoperations in the adrenal area are contemplated as was the case in three of our patients. These operations have been facilitated by using an approach opposite to the previous one so that the adrenals can be reached through unscarred tissue.

As our experience has developed, and testing procedures have become more sophisticated, the efficiency and safety of adrenalectomy has increased. It seems possible to approach the ultimate cooperation between endocrinologist and surgeon: perfection in diagnosis, absolute localization of disease, and surgery with minimal complications, no mortality, and excellent results. It is tempting for the surgeon to claim credit for the paucity of operative complications in this series. However, it is very plain that some of the major reasons why surgery of aldosteronism is far safer than adrenalectomy for advanced cancer or Cushing's disease is because the metabolic abnormality of primary aldosteronism can be overcome prior to operation and associated problems can be minimized. When the physiology of the operated patient is as predictable as it has become for us in this disease, problems can be corrected before they become serious; and excessive therapeutic reactions to physiologic changes can be avoided.

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DISCUSSION

DR. WILLIAM SILEN (Boston): In 1966, as Dr. Hunt mentioned, we reported with Dr. Biglieri before this society a group of 24 patients with hyperaldosteronism. We suggested, on the basis of differential levels of aldosterone determined on blood taken from the inferior vena cava and directly from the adrenal vein at operation in a small number of patients, that preoperative catheterization might be of value in determining the side of the lesion. Since then we have found that indeed such determinations are in most cases correctly predictive and enable the surgeon to confine his activities to the side of the lesion.

Therefore, whereas we had in 1966 advocated transabdominal bilateral adrenal exploration, we would now agree with Dr. Hunt that more sophisticated radiologic techniques and adrenal vein catheterization with assay of aldosterone make unilateral operation feasible in most cases. We happen to be blessed with a superb radiologist who can catheterize the adrenal veins essentially 100% of the time. If doubt exists, however, on the basis of catheterization data and/or the scan, then I think that the bilateral transabdominal exploration still has probably a place.

One other caution, however, in our recent experience. Namely, retrograde venous injection of dye, although it may outline the lesion and has done so in our hands, is potentially hazardous and is probably unnecessary.

There are two reasons for this: First, that adrenal infarction of the normal adrenal can occur if retrograde injection is done and therefore render the patient susceptible to adrenal insufficiency after removal of the contralateral abnormal gland; and secondly, infarction of the affected gland can make its subsequent removal extremely difficult from a technical standpoint because of severe fibrosis and reaction in the surrounding tissue.

DR. RICHARD H. EGDAHL (Boston): At Boston University, we have considerable interest in this disease and our experience pretty much bears out his conclusions.

(Slide) One of the things we found, and this goes along with what Tom Hunt said, is that we must look on this disease of primary aldosteronism as perhaps even more complicated than has ever been suggested. It is more like hyperparathyroidism and the problem of differentiating hyperplasia and adenoma.

We have now studied a fairly large number of cases. We have almost 90% good results within the first three months for the standard syndrome of solitary adenoma; 30% are hypertensive at one year.

However, it is ominous that if you follow these patients for five years, about 50% of them are hypertensive and this in the presence of normal adosterone secretion rates. In other words, at 5 years post-op, the incidence of hypertension in patients who appear to be cured by removal of a solitary adenoma seems very much higher than would occur in the normal population. This is reminiscent of a paper from P&S long range results following presumable curative surgery for islet cell adenoma.

So there's something funny about the long range followup solitary adenomas in terms of recurrent hypertension.

(Slide) This shows a point of disagreement that we may have with some of the other groups concerning results for bilateral nodular hyperplasia as compared to solitary to tumors. Approximately 30% appear to be cured of hypertension following removal of one adrenal with a dominant nodule or by bilateral adrenalectomy.

The fascinating thing is that in 30% of the cases with hyperplasia followed for five years, the cure of hypertension seems to hold up. Quite clearly, the patients had hyperaldosteronism and were severely sick from their hypertension. I think it's going to be ten or more years for us to know the full spectrum of this complicated disease.

(Slide) This simply points out that measurement of plasma aldosterone with the radioimmunoassay technique, along with sampling of plasma renin, makes it possible to do a complete diagnostic workup for aldosteronism on ambulatory patients. So the patients who has high aldosterone levels in peripheral blood and low renins, has primary aldosteronism.

I think this means we can begin to develop criteria and look at the necessity for hospitalization in the diagnostic workup of this rather complex endocrinopathy. This observation has pertinence to issues of quality and cost, and to PSROs and their functions of utilization review and medical audit.

DR. THOMAS K. HUNT (Closing discussion): We agree in general with the comments that have been made. We have not been as good at adrenal vein catheterization as has the Boston Group, and we're jealous of your results. We've learned to be wary of interpreting the results of a unilateral catheterization. On one occasion, a unilateral catheterization with a good step-up of aldosterone concentration led us into believing there was an adenoma on one side, and a potentially useless adrenalectomy was done in a patient with bilateral hyperplasia.

We have not done the angiography because there is a real chance that the normal gland can be infarcted and instead of having a cured patient with a normal adrenal function postoperatively, you have an Addisonian.

Our indications for operation are very much as Dr. Egdahl suggested. In general, we operate on those patients with biochemical evidence of adenoma whose blood pressure cannot be controlled with less than 150 mg of spironolactone a day because over that level the side effects become very difficult, particularly in men. We also select those patients who on any dose of spironolactone show deterioration of target organ function. A segmental resection of one adrenal to remove just the adenoma has been suggested recently, but we wonder, based on our observation that the adenomatous adrenal is often also hyperplastic, if leaving behind this hyperplastic tissue might have functional significance and lead to a quick return of the syndrome.

Secondly, can an adenoma with hyperplasia in the same gland foretell the future that the other gland will be similarly affected in future years with return of the syndrome? So far, our followup of almost fifteen years has not disclosed such a trend.

Thirdly, what do we do with hyperplasia since obviously even with the adrenals removed, there's still some stimulus to hypertension.

I think all these questions must be answered before we can really promise the perfection that I hinted at.

The Early Diagnosis of Medullary Carcinoma of the Thyroid Gland in Patients with Multiple Endocrine Neoplasia Type II

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Pentagastrin is a potent stimulator of thyrocalcitonin secretion from "C" cells. Since medullary carcinoma of the thyroid gland (MCT) is a tumor composed of "C" cells, pentagastrin was used to screen a large kindred with multiple endocrine neoplasia type II (MCT, pheochromocytoma (s), and parathyroid hyperplasia). Four children with no thyroid abnormalities evident on physical examination, with negative thyroid scans, and with normal levels of plasma thyrocalcitonin both before and after calcium infusion, were found to have elevated peripheral levels of this hormone following pentagastrin injection. All four children were found to have very small foci of MCT, in both thyroid lobes at the time of total thyroidectomy. Pentagastrin stimulation used conjointly with selective catheterization of the inferior thyroid vein provided even greater diagnostic accuracy in detecting elevations in thyrocalcitonin secretion. This test has great diagnostic utility, especially in screening patients with multiple endocrine neoplasia type II.

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IN 1959, Hazard, Hawk, and Crile[6] described medullary carcinoma of the thyroid gland (MCT), a tumor which has subsequently been shown to account for 5-10% of all thyroid malignancies. Clinically, it presents either sporadically or in a familial pattern inherited as a Mendelian dominant trait and associated with parathyroid hyperplasia and pheochromocytoma (s). This syndrome has been referred to as multiple endocrine neoplasia, type II (MEN-II).[17] Although genetically there seems to be complete penetrance, there is variable expressivity and affected patients usually do not develop all three components of the disease. Almost all, however, develop MCT, and it is this lesion that develops earliest[9] and is most life threatening. It has been shown that medullary carcinomas of the thyroid are composed of parafollicular or "C" cells which apparently arise from the neural crest. These tumor cells are capable of great biosynthetic activity, and have been shown to secrete ACTH,[12] prostaglandins,[21] histaminase,[1] serotonin,[13] and thyrocalcitonin (TCT).[18] It is the TCT which has proved to be of greatest clinical importance because it has served as a tumor marker for MCT. Measurement of TCT in kindreds with MEN-II has been especially helpful because an elevated serum concentration of this hormone often provides the diagnosis of MCT before the lesion is palpable clinically or is demonstrable by thyroid scanning.[9,18] Calcium,[11] glucagon,[11] and pentagastrin[7] have all been shown to stimulate the secretion of TCT from medullary carcinoma cells, and have thereby increased the clinician's ability to diagnose this malignancy. This report demonstrates the usefulness of pentagastrin, a potent and reliable

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stimulator of TCT release in screening asymptomatic family members with MEN-II for medullary carcinoma of the thyroid gland. Of special utility has been the combination of selective venous catheterization and pentagastrin stimulation in diagnosing MCT early, and in localizing metastatic disease in patients with recurrent MCT.

Materials and Methods

Patients: The patients studied were from a large kindred with multiple endocrine neoplasia, type II. All diagnostic tests were performed on the Clinical Research Units of the Duke University Medical Center or the North Carolina Memorial Hospital. The calcium and pentagastrin provocative tests were performed on separate days within a 3 to 5 day hospitalization, while the patients were receiving a diet constant in calcium (800 mg elemental calcium a day). The order in which the tests were administered was varied so that some of the patients received the calcium infusion test initially, (followed by the pentagastrin test), while others received the pentagastrin test initially, (followed by the calcium infusion test). The calcium infusion test was begun at 8:00 a.m. after an overnight fast. A total dose of 15 mg/kg of calcium ion was administered by intravenous infusion of calcium gluconate in 500 ml of 0.15 M NaCl over a 4-hr period. Blood samples were collected through an indwelling needle in the antecubital vein at 0, 15, 30, 60, 120, 180, and 240 minutes for subsequent determinations of calcium, phosphate, and TCT. Samples for TCT analysis were collected in heparinized tubes, chilled, and the plasma promptly separated and frozen at −20 C until assayed. Serum calcium[3] and phosphate[4] concentrations were determined by the automated methods of Gitelman.

Pentagastrin stimulation tests were begun at 8:00 a.m. after an overnight fast. After collection of baseline blood samples, patients were given pentagastrin (Peptavlon): a gift from Ayerst Laboratory, in a dose of 0.5 mcg/kg by rapid infusion injection (over 5-10 seconds) in 2-4 ml of 0.15 M NaCl. Blood samples were taken at 0, 1, 2, 3, 5, 10, 15, 30, and 60 minutes. Approximately 30 seconds after the injection, a majority of patients noticed mild epigastric pain which usually persisted for 45-60 seconds. No serious side effects were encountered.

Other studies performed during hospitalization included a complete blood count, blood chemistry analysis, urinalysis, and 24-hour urinary catecholamine determination. All patients had a chest X-ray, a metabolic bone survey, and an ^{131}I thyroid scan and 24-hour uptake.

Selective venous catheterization: In two patients, an inferior thyroid vein was catheterized using the Muller guided catheter system as described by Doppman.[2] Blood was sampled from an inferior thyroid vein and simultaneously from a peripheral antecubital vein before and at 1, 2, 3, 5, and 10 minutes following the intravenous injection of pentagastrin. The blood samples were placed in heparinized tubes, immediately chilled, and the plasma separated for subsequent TCT determination.

In one patient who had previously undergone total thyroidectomy for medullary carcinoma and who had one year later demonstrated an elevated level of TCT following pentagastrin injection, four catheters were placed simultaneously into the left inferior thyroid vein, the hepatic vein, the basilic vein, and the root of the aorta. Before and at 1, 2, 3, 5, and 10 minutes following the injection of pentagastrin, blood samples were collected in heparinized tubes from each of these veins. Subsequently the plasma was separated from the chilled tubes and frozen for TCT determination.

Detection of thyrocalcitonin in plasma: The radioimmunoassay used to detect thyrocalcitonin in the plasma of patients studied has been previously described.[8] The lower limit of sensitivity of the assay in human plasma was 240 pg/ml. Using the assay as described, we have been unable to detect TCT in any plasma samples from normal subjects, even after injection of pentagastrin.

Radioimmunoassay of thyroid glands for thyrocalcitonin content: Fresh tissue slices removed from the upper, middle, and lower portions of each thyroid lobe were taken at the time of surgery and homogenized in 0.1 N HCl in a volume of 10 ml/gm. The material was then centrifuged at 15,000 rpm for 10 minutes and the supernatant was radioimmunoassayed for thyrocalcitonin content.[8]

Histologic studies: At the time of total thyroidectomy, additional tissue slices from the upper, middle, and lower parts of each lobe were taken. Half of these slices were fixed in Zenker's formol solution for routine pathologic evaluation. This fixed material was subsequently embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The adjacent portions of tissue were fixed in buffered formalin and washed three times in phosphate buffered saline. This material was stained with the immunoperoxidase bridge technic by Dr. T. C. Peng to localize thyrocalcitonin in "C" cells.This technic which depends upon the binding of a specific anti-TCT antibody to the surface of cells containing TCT has been previously described.[15]

Surgical Procedure

Once a patient had demonstrated an elevated level of thyrocalcitonin following pentagastrin stimulation, they were advised to undergo a total thyroidectomy. Under general anesthesia, a standard anterior cervical incision was made and a total thyroidectomy was performed. Lymph nodes as far as the carotid sheaths bilaterally were removed with the thyroid mass. Great care was taken not to compromise the vascularity or the substance of the parathyroid glands.

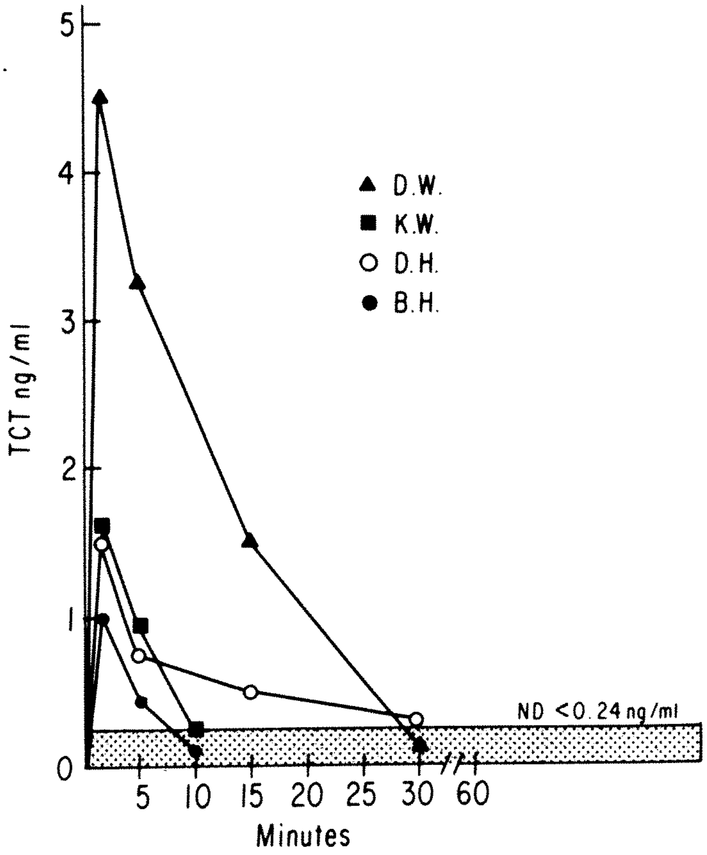

FIG. 1. Thyrocalcitonin response to pentagastrin stimulation in four children (D.W., K.W., D.H., and B.H.) with a family history of multiple endocrine neoplasia type II.

Results

Over the last two years a total of 40 members from a large kindred with multiple endocrine neoplasia type II have been screened. During the first year of screening, three children, D.W., B.H., and D.H., ages 13 to 17, were diagnosed as having medullary carcinoma of the thyroid gland. None of these children had detectable TCT in the peripheral blood, even in response to a calcium infusion. However, all had elevated levels of thyrocalcitonin (greater than 1.0 ng/ml) within 1 to 3 minutes following pentagastrin injection (Table 1 and Fig. 1). During the second year of study, the fourth patient (K.W.) had an elevated level of TCT following pentagastrin injection (Table 1 and Fig. 1). He had shown a negative response to both calcium infusion and pentagastrin injection the previous year and remained unresponsive to calcium stimulation the second year. None of these four patients had palpable thyroid nodules or evidence of thyroid lesions on ^{131}I scanning.

The operative procedure used in these children was a total thyroidectomy combined with removal of lymphatic tissue laterally as far as the carotid sheaths. At the time of surgery no mass was palpable in either thyroid lobe in 2 of the 4 patients, however lesions were visable when the thyroid parenchyma was sectioned following removal of the gland from the neck (Fig. 5). In the remaining two patients small thyroid nodules were noted at surgery in the upper regions in each thyroid lobe. Only one patient (D.W.) had tumor extending to the thyroid capsule. In no patient was tumor detected in the lymph nodes adjacent to the thyroid gland.

In addition to the tumor foci which were grossly visible in the thyroid lobes of each patient, there were smaller microscopic foci of "C" cell clusters. The content of thyrocalcitonin in the thyroid gland of each patient was determined by radioimmunoassay. None of the sections

TABLE 1. *Patients Diagnosed as Having Medullary Carcinoma of the Thyroid Gland by Pentagastrin (Pg) Stimulation*

Patient	Baseline TCT Level*	TCT Peak* With Ca^{++} Infusion	TCT Peak* With Pg Stimulation (Peripheral Vein)	TCT Peak With Pg Stimulation (Thyroid Vein)	Clinical Findings	Findings at Surgery
D.W.	N.D.	N.D.	4.5 ± 1.3	N.T.	No Thyroid Nodule, ^{131}I Thyroid Scan Negative	Macroscopic Bilateral MCT
K.W.	N.D.	N.D.	1.4 ± 0.5	18	No Thyroid Nodule, ^{131}I Thyroid Scan Negative	Macroscopic Bilateral MCT
D.H.	N.D.	N.D.	1.5 ± 0.6	N.T.	No Thyroid Nodule, ^{131}I Thyroid Scan Negative	Macroscopic Bilateral MCT
B.H.	N.D.	N.D.	1.0 ± 0.1	N.T.	No Thyroid Nodule, ^{131}I Thyroid Scan Negative	Macroscopic Bilateral MCT
C.P.	N.D.	N.D.	N.D.	9.6 ± 2.1	No Thyroid Nodule, ^{131}I Thyroid Scan Negative	No. Mascroscopic Disease. "C" Cell Hyperplasia Microscopically.

N.D. = not detectable (<240 pg/ml)
*Values of TCT expressed in ng/ml ±S.E.M.

assayed contained grossly visable tumor. As can be seen in Table 2, the highest levels of TCT were detected in grossly normal tissue from each patient, mainly in the middle and upper regions of the thyroid lobes. The values ranged from 10 to 7200 ng per gram of tissue.This is consistent with the findings of Wolfe, and associates.[20]

In all 4 patients there was no detectable thyrocalcitonin following pentagastrin stimulation in the immediate postoperative period.

One patient (B.H.) was hypercalcemic preoperatively, and at surgery was found to have two grossly enlarged and microscopically hyperplastic parathyroid glands. Another patient (D.W.) had microscopic evidence of parathyroid hyperplasia, although she had no elevation in her serum calcium concentration preoperatively. Two other patients, (K.W. and D.H.), had no hypercalcemia preoperatively and their parathyroid glands appeared normal both to gross and microscopic examination.

All 4 patients are now on thyroid replacement therapy but none requires Vitamin D or calcium supplement.

Selective venous catheterization: In patient K.W., who was known to have an elevated peripheral level of TCT following pentagastrin injection, a selective venous catheterization study was performed just prior to his surgery. As demonstrated in Fig. 2, a markedly higher concentration of thyrocalcitonin was detected in the right inferior thyroid vein following pentagastrin injection than was measurable in the peripheral vein sampled concurrently.

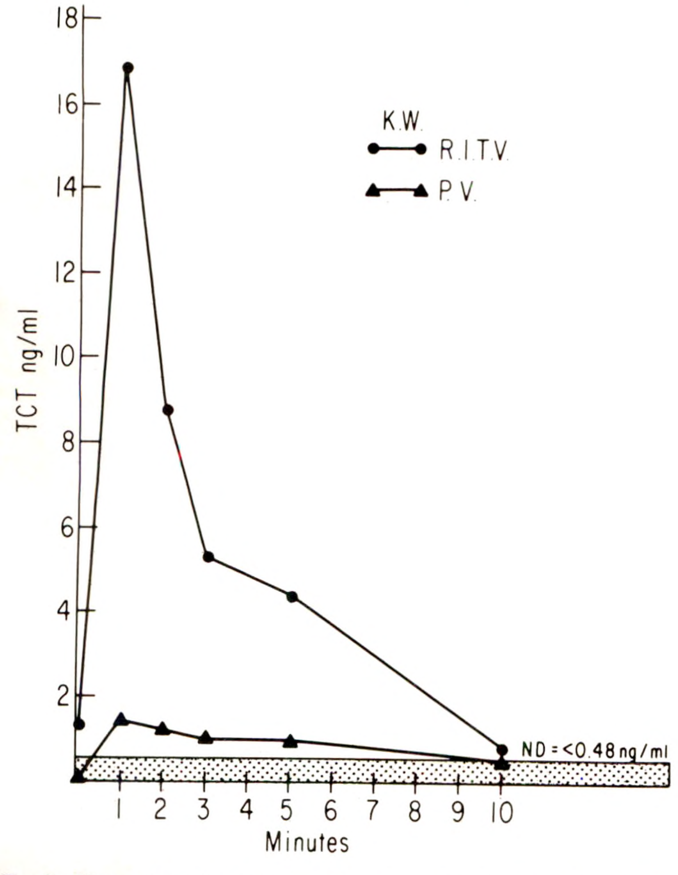

FIG. 2. Thyrocalcitonin response to pentagastrin stimulation in patient K.W. Note the higher level of TCT in the right inferior thyroid vein compared to the level in a peripheral vein.

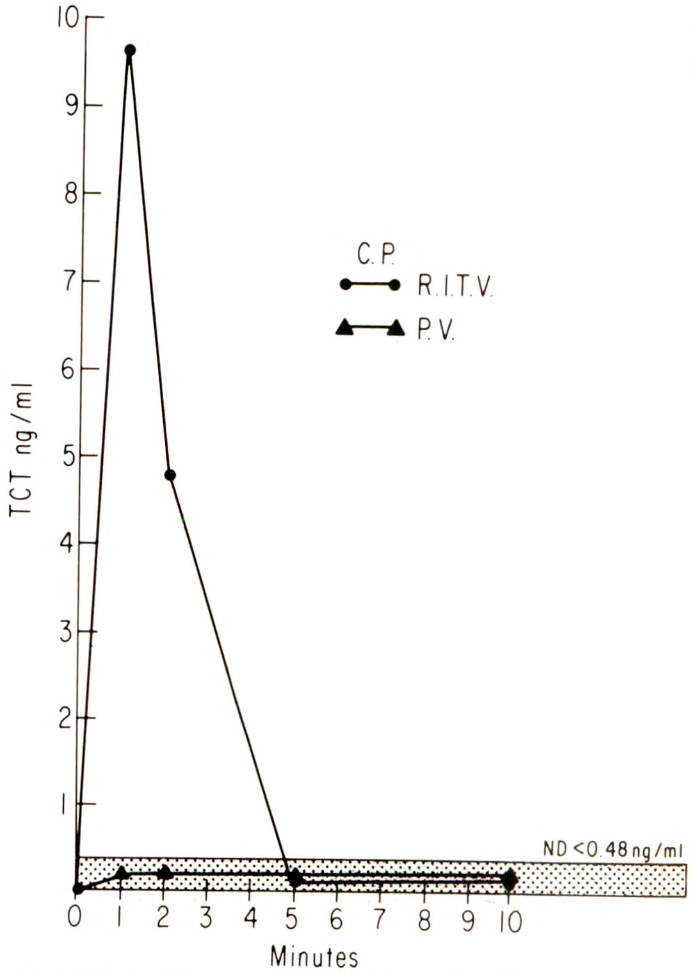

FIG. 3. Thyrocalcitonin response to pentagastrin stimulation in patient C.P. Note the absence of TCT elevation in the peripheral blood following pentagastrin stimulation. An elevated TCT level is only detected in the right inferior thyroid vein.

Patient C.P., a 40-year-old man, had no measurable TCT level in the peripheral blood following pentagastrin stimulation. However, because of his positive family history he underwent selective venous catheterization and pentagastrin stimulation. As shown in Fig. 3, no TCT was detectable in the antecubital vein during the pentagastrin stimulation test, but there was a peak value of 9.8 ng/ml of TCT in the right inferior thyroid vein 1 minute following pentagastrin stimulation. A total thyroidectomy was performed and no macroscopic tumor was visualized in the sectioned thyroid gland at surgery or subsequently by pathological examination. On microscopic examination of H and E stained sections, however, foci of "C" cell hyperplasia were noted (Fig. 6). Furthermore, on immunoperoxidase staining, clusters of "C" cells were readily detected, due to their specific content of TCT. Radioimmunoassay measurement of

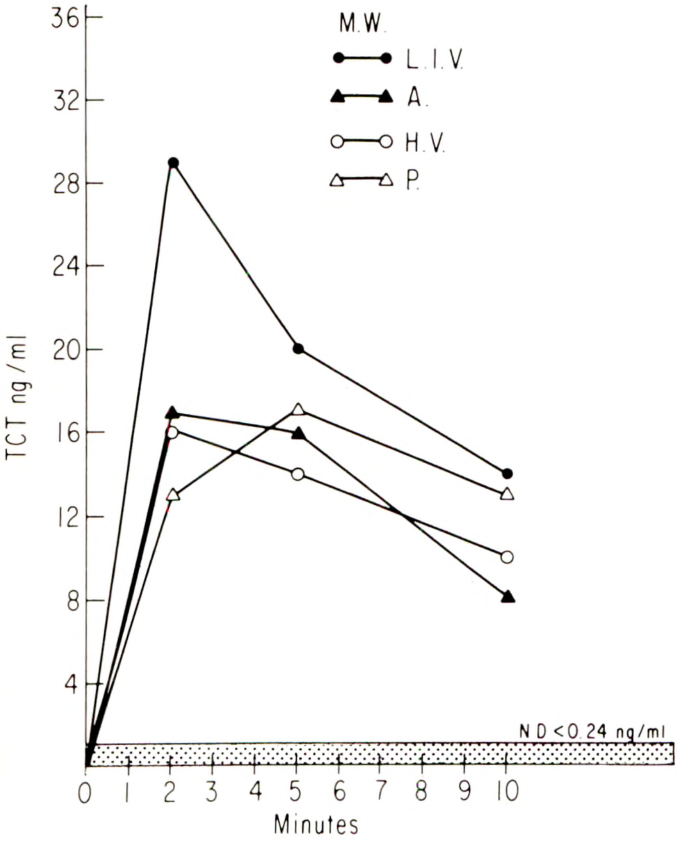

FIG. 4. Thyrocalcitonin response to pentagastrin stimulation in patient M.W. Note the highest level of TCT in blood sampled from the left innominate vein.

portions of the thyroid gland removed at surgery demonstrated abnormally high concentrations of TCT in the thyroid glands, especially in the middle regions of both lobes (Table 2). Two parathyroid glands were removed from patient C.P.; one was enlarged and one was of normal size grossly; however, both showed absence of fat cells and histological characteristics of parathyroid hyperplasia.

Patient M.W. had a total thyroidectomy in July 1973 for medullary carcinoma of the thyroid gland. Preoperatively, he had a basal plasma level of thyrocalcitonin of 51 ng/ml which increased to 352 ng/ml at 2 minutes following pentagastrin stimulation. Postoperatively, he had no detectable TCT in the peripheral blood following pentagastrin stimulation. One year following surgery he was re-tested, and although the basal level of TCT was still undetectable, there was an elevated level of 17 ng/ml in peripheral venous plasma following pentagastrin stimulation. In an attempt to localize the recurrent tumor, catheters were selectively placed in the left innominate vein, the hepatic vein, a peripheral vein, and the root of the aorta. As can be seen in Fig. 4, the highest concentration of TCT following pentagastrin injection was detected in the left innominate vein. Accordingly, the patient's neck was re-explored and he was found to have lymph nodes containing tumor in the left side of the neck. A left radical neck dissection was performed. There was no disease by palpation in the right neck and frozen section examination of random nodes revealed no evidence of metastatic disease there.

TABLE 2. *TCT Concentration (ng/gm)* in the Thyroid Glands of Patients With MCT Diagnosed by Pentagastrin Stimulation*

Thyroid lobe	D.W.	K.W.	D.H.	B.H.	C.P.
R Upper	190	64	7200	2500	85
R Middle	70	483	870	71	5030
R Lower	70	10	70	85	135
L Upper	1300	10	75	2300	77
L Middle	70	566	1200	260	5400
L Lower	70	420	70	470	650

*TCT concentration in the thyroid tissue of normal individuals = 10 to 300 ng/gm.

Discussion

A total of 40 patients were evaluated in the initial phase of this study. A comparison of the TCT response both to calcium infusion and pentagastrin injection was assessed and has been previously reported.[8] Briefly, it was found that pentagastrin was a much more potent stimulator of thyrocalcitonin secretion from MCT than calcium infusion. Following the injection of pentagastrin (0.5 mcg/kg) the peak TCT response occurred at approximately 2 minutes, compared to a peak response at 30 minutes following initiation of the calcium infusion test (15 mg/kg/4 hours). Furthermore, the peak TCT response following pentagastrin was two to four fold higher than that following calcium infusion. These two obvious advantages combined with the rapidity and simplicity of pentagastrin administration, currently make it the agent of choice in screening for medullary carcinoma of the thyroid gland. Our interest in the current study was to determine if pentagastrin was effective in detecting MCT in patients with preclinical disease. That pentagastrin was effective in this regard was readily demonstrated by four patients (D.W., K.W., D.H., and B.H.) in this study. Medullary carcinoma of the thyroid gland was diagnosed in each by demonstrating an elevated concentration of TCT in the peripheral blood following pentagastrin stimulation. The sensitivity of this diagnostic test is impressive when one considers the absence of thyroid nodules on physical examination, the failure to demonstrate lesions by thyroid scan, the actual small size of the malignant primary tumors and the absence of metastatic disease in regional lymph nodes.

As demonstrated previously in selective venous catheterization studies in patients with parathyroid adenomas, higher concentrations of parathyroid hormone are detectable in the venous effluent closest to the source of its production.[16,19] Similar observations have been made in patients with medullary carcinoma of the thyroid gland.[5,14] A combination of pentagastrin stimu-

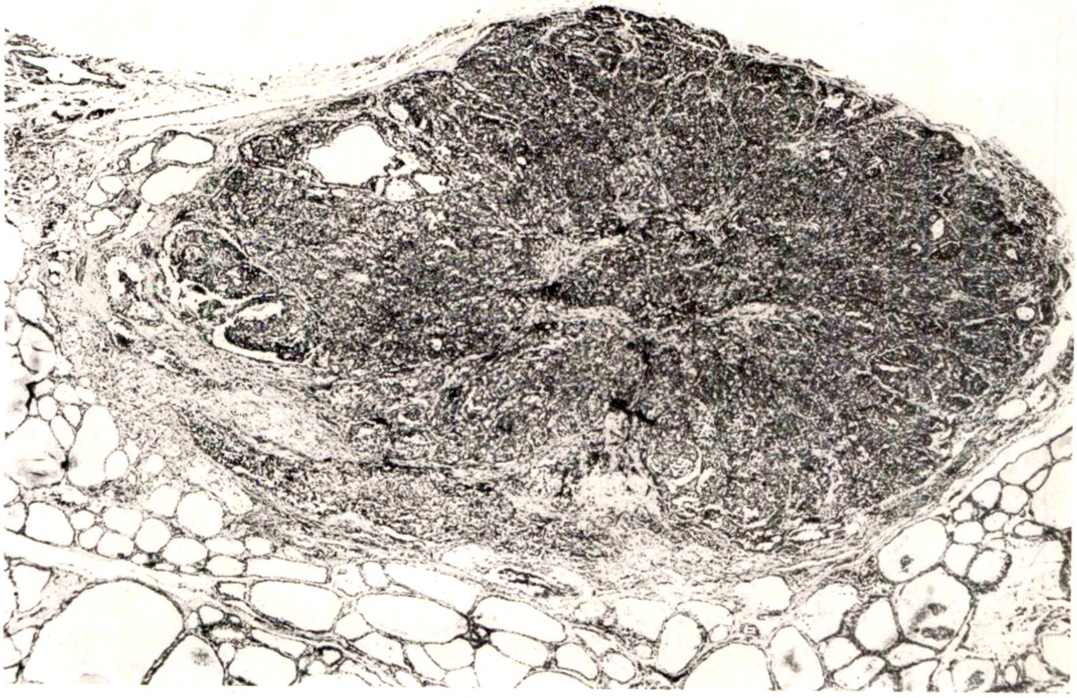

FIG. 5. Grossly visible medullary carcinoma nodule in the right thyroid lobe of patient K.W. Hematoxylin and eosin, original magnification ×25.

lation and selective venous catheterization provides a very sensitive method for diagnosing primary medullary carcinoma of the thyroid gland. As demonstrated by patient C.P. in this study, thyrocalcitonin elevation occurred only in the catheterized thyroid vein and not in the peripheral vein, and only following pentagastrin stimulation. We have studied 6 other persons, using the selective catheterization technic combined with pentagastrin stimulation, and have not detected elevated levels of TCT in either the peripheral veins or the

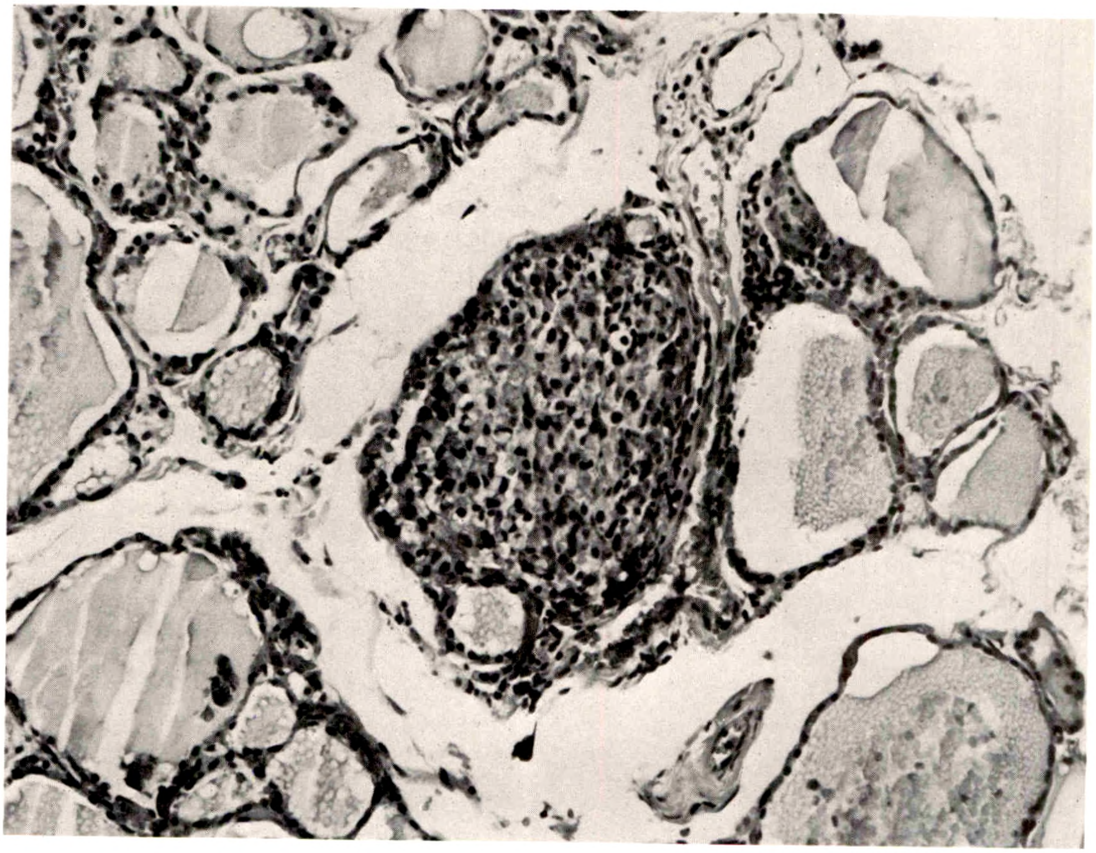

FIG. 6. A focus of "C" cell hyperplasia demonstrable in the thyroid gland of patient C.P. Hematoxylin and eosin, original magnification ×190.

catheterized neck veins. Three of these patients had benign thyroid neoplasms which were resected at surgery, and the remaining 3 patients were members of the MEN II kindred with as yet no evidence of MCT.

In patients who have undergone thyroidectomy for medullary carcinoma and subsequently developed elevated levels of TCT with or without pentagastrin stimulation, selective venous catheterization is advantageous in localizing the site of recurrence. In one of the patients in our study (M.W.), there was no detectable level of TCT in the aortic root draining the pulmonary bed, in the hepatic vein draining the liver, in the innominate vein draining the neck, or in the antecubital vein. Following pentagastrin injection, however, there was a marked increase of TCT detectable in the left innominate vein. There were increased levels of TCT in the other sites sampled, but they were all in the same general range and none was as high as the innominate vein level. At subsequent surgery the patient was found to have metastatic disease involving the left side of the neck as predicted by the assay results. Although others have used selective venous catheterization alone to localize sites of medullary carcinoma,[5,14] the combination of this technic with pentagastrin stimulation, especially when the effluent from several organs is simultaneously sampled appears especially effective in localizing metastatic disease.

Our current method of following patients with a family history of multiple endocrine neoplasia type II is to perform pentagastrin stimulation tests yearly in all children above the age of 10 years. Should the level of TCT in peripheral plasma be 1.0 ng/ml or greater then the patient should undergo total thyroidectomy. Should the peak TCT level be between 0.5 and 1.0 ng/ml following pentagastrin injection then we favor using selective thyroid venous catheterization combined with pentagastrin stimulation to detect MCT. A single catheter is used to sample either inferior thyroid vein concomitantly with the peripheral vein following pentagastrin injection. At the time of surgery an attempt is made to remove all lymph node tissue laterally as far as the carotid sheaths. If metastatic disease is present grossly in the neck, a neck dissection is performed.

In the immediate postoperative period, the pentagastrin stimulation test is again performed, samples being obtained only from a peripheral vein. If this is negative, patients are followed at yearly intervals with pentagastrin stimulation tests and peripheral sampling. Should an elevation in TCT occur during one of these tests, then the pentagastrin injection combined with sampling from multiple sites is performed to localize metastatic disease.

The pentagastrin test is an extremely sensitive means for diagnosing medullary carcinoma of the thyroid gland. Its combination with selective venous catheterization technics provides a powerful tool both for diagnosis of medullary carcinoma and localization of metastatic foci.

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DISCUSSION

DR. MELVIN A. BLOCK (Detroit): We too have been utilizing intravenous pentagastrin as a provocative test for the detection of medullary thyroid carcinoma, following the reports of Drs. Hennessy and Wells and their colleagues. Dr. Charles E. Jackson of our group has carried out this test on 125 occasions on 90 different patients, most being members of families subject to medullary thyroid carcinoma.

We agree that intravenous pentagastrin provides the most sensitive test now available for the detection of this lesion. It is a safe and rapid test. Most of our patients experience fleeting nausea but only three have vomited. It may be feasible to utilize this examination in the field by going out to members of families in their homes.

A problem we have encountered relates to finding elevated levels of serum calcitonin, frequently only slight, after administration of pentagastrin as a provocative agent late following operation considered to have eradicated medullary thyroid carcinoma in the neck. It almost seems that the test can be too sensitive. Such patients have been asymptomatic and there has been no other obvious evidence of the presence of medullary thyroid carcinoma.

Thus, one patient who has no evidence of residual or metastatic disease 11 years after his neck operation has a borderline elevation of the serum calcitonin (0.59 ng/ml) after the intravenous infusion of calcium but an elevation to 3.8 ng/ml after the intravenous injection of pentagastrin.

The use of selective venous catheterization collections for radioimmunoassays has not always been helpful in localizing metastases for these patients. To date we follow the policy of following these patients regularly. Undoubtedly, they do have foci of residual medullary thyroid carcinoma but we have been reluctant to advise anything more than continued periodic examinations.

I would like to ask Dr. Wells if he has had a similar experience in postoperative patients and what their policy is relative to this problem.

DR. TIMOTHY S. HARRISON (Ann Arbor, Michigan): I think this is a fine study by Dr. Wells and his seven collaborators and I rise only to indicate that studies such as he describes have been particularly useful in a series of 36 pheochromocytoma patients. Some were felt to have sporadic pheochromocytoma and in two patients it was only by demonstrating elevated serum calcitonin that occult medullary thyroid carcinoma came into view. At thyroidectomy, both patients' medullary carcinomas were multicentric but still confined to the thyroid gland.

We think that the stimulated value of serum calcitonin release is certainly established as a screening test and that one should look particularly carefully at the affected families from which the symptomatic kindred have come. In addition, screening of all pheochromacytoma patients should be done to study the possibility of there being present occult medullary carcinoma of the thyroid.

MEA II is a much broader problem than that of medullary carcinoma alone and I would be interested, Dr. Wells, in hearing from you about the frequency and morphology of the parathyroid changes you've seen and would you also comment on the adrenal medullary lesions.

The Mayo Clinic, in particular, has described, as others have before them, an adrenal medullary hyperplasia in MEA II which has an unusual secretory pattern characteristized biochemically by an increased secretion of vanillyl mandelic acid only. I wonder if you've seen these lesions.

DR. EDWARD S. JUDD, JR. (Rochester, Minnesota): Mr. Chairman, when we're confronted with the Sipple syndrome, in its entirety, I think all of us know what to do. However, there are times when the syndrome is quite incomplete and not all symptoms are presented.

I would like to ask the authors what their recommendation is when they're operating for a medullary carcinoma of the thyroid and they visualize four apparently entirely normal looking parathyroid glands?

Have they progressed far enough in their diagnostic acumen to recommend to us on the basis of probability alone whether we should proceed at once and remove the four normal looking parathyroid glands?

DR. BENJAMIN F. RUSH, JR. (Newark, New Jersey): I'd like to mention a small case history which perhaps supports the findings of Dr. Wells and his colleagues. It also raises a question.

In 1968, at the University of Kentucky, we encountered a kindred of a sister and two brothers with Sipple Syndrome.

All members of this group had at least two endocrine components of the syndrome, all had medullary carcinoma of the thyroid; all had pheochromocytomas and one member had parathyroid hyperplasia.

Since we explored the abdomens of all three patients, we noted that all three had metastatic lesions in their liver from medullary carcinoma of the thyroid.

The woman in the kindred had a child approximately age four at this point and after a good deal of soulsearching, it was finally decided without the benefit of any but statistical evidence to explore this child's thyroid.

Exploration revealed a medullary carcinoma of the thyroid occupying both lobes as well as a metastatic lesion in the neck. This experience led us to reflect as to just when these lesions do begin in the thyroid and whether they may not actually be present in these children from birth.

DR. CHARLES ECKERT (Albany, New York): When Dr. Block presented his paper on this subject before this group, Sam Powers discussed it and described a similar kindred that we have had in Albany. Of interest is the fact that five of the patients with medullary carcinoma who have had total thyroidectomy over five years ago, who have no evidence of disease at present, have elevated levels of calcitonin in their blood without provocative tests.

I think this confirms Dr. Block's observation and I wonder whether the present authors have had similar experience.

DR. SAMUEL A. WELLS, JR. (Closing discussion): In answer to Dr. Block's first question, we also had noted that patients experienced some discomfort following the intravenous injection of pentagastrin. Usually patients experience some low substernal and epigastric burning pain that lasts for about 30–40 seconds after receiving the injection. Theoretically the test could be used in the field for screening asymptomatic family members. Since the peak response of thyrocalcitonin following pentagastrin stimulation occurs within 2–5 minutes, the entire test could easily be completed in 10 minutes. This screening test is extremely sensitive in detecting early medullary carcinoma of the thyroid gland as we have demonstrated.

Dr. Block's second question relates to the management of patients with persistently elevated levels of serum thyrocalcitonin following resection of medullary thyroid carcinoma. After we have operated on patients we usually follow them at six month intervals performing a pentagastrin test to detect elevated levels of thyrocalcitonin. When a patient who has had previously negative responses suddenly develops an elevated level of thyrocalcitonin following pentagastrin stimulation, we perform selective venous catheterization pentagastrin stimulation in an attempt to localize the site of recurrent disease. If it appears to be localized to the neck, then we feel that the patient should undergo repeat neck exploration with resection of recurrent tumor. I will admit, however, that the test is very sensitive and will detect the presence of disease long before it is detectable by clinical or radiological means. We are most bothered by those individuals who have definite but very minimal elevations of pentagastrin stimulated thyrocalcitonin because we know that their recurrent lesions will be small and perhaps difficult to locate surgically.

We are now following two patients who have been operated upon as long as 15 years ago. Both patients have had minimally elevated levels of thyrocalcitonin which have not changed markedly over the last three years. Both patients have metastatic disease in anatomical areas other than the neck and are not surgical candidates.

In answer to Dr. Harrison's question, I think it would be very wise to perform pentagastrin stimulation tests on all patients with pheochromocytomas and especially if the patients have bilateral lesions. Conversely, I feel that patients with medullary carcinoma of the thyroid gland must also be screened for the presence of pheochromocytomas. In patients with multiple endocrine neoplasia type II, the pheochromocytoma must be diagnosed first and treated prior to neck exploration.

Our series now includes 40 patients who have been operated upon for multiple endocrine neoplasia type II. Of this number, 26 patients have had evidence of parathyroid hyperplasia. By that I mean that 26 patients had enlarged parathyroid glands found at surgery. We have termed the parathyroid disease that occurs in this syndrome, pseudonodular hyperplasia. A few of the patients in our series had neck explorations and resection of parathyroid lesions prior to the time that we saw them. They subsequently became hypercalcemic and required second neck explorations and resection of other hyperfunctional parathyroid tissue.

Of the pheochromocytomas that we have seen, almost all secreted elevated levels of VMA, epinephrine and norepinephrine. Some have been diagnosed only by provocative testing, however.

Regarding Dr. Judd's comments about the management of the parathyroid disease, I think this can be a very difficult problem. In two of the patients whom we have had in our series we have performed parathyroid transplantations at the time of the initial neck surgery. All the parathyroid glands were removed from the neck and two of the smaller ones were transplanted into a muscle bed in the forearm by a technique which we have previously described. Both patients are doing well now, more than a year after transplantation, and both have normal serum calcium concentrations with no replacement therapy.

Routinely at surgery we make every attempt to find all four parathyroid glands. If a parathyroid gland is enlarged, it is removed. If all four glands are enlarged they are all removed and the parathyroid autotransplantation is done. In the past we have left normal size parathyroid tissue which is normal histologically by biopsy, but have marked each gland with a suture so that it can be found subsequently should hypercalcemia develop and neck exploration be required.

In answer to Dr. Rush's question, I am not sure how early this disease actually starts in the affected family members. There has been one case reported of a child who had the disease at the age of five years. As our current paper demonstrates, we have detected disease most frequently in patients during their teenage years. Also, as demonstrated in this paper, we diagnosed one patient with C-cell hyperplasia.

Dr. Eckert, we have made every attempt to diagnose this disease as early as possible. I think that if the pentagastrin stimulation test is done serially, beginning at the age of eight or ten years and every six months or 12 months thereafter, a child can be diagnosed as having medullary carcinoma of the thyroid gland before it becomes manifest clinically. We actually begin the pentagastrin study in younger family members of this large kindred because one 15-year-old child presented with widespread metastatic medullary carcinoma of the thyroid gland and died two years later.

All the children in our series who have the diagnosis of medullary thyroid carcinoma made by pentagastrin stimulation and who have subsequently undergone total thyroidectomies have been negative to pentagastrin stimulation since their surgery. Admittedly, this is a short followup time and we will be most anxious to see how these children do over the next several years.

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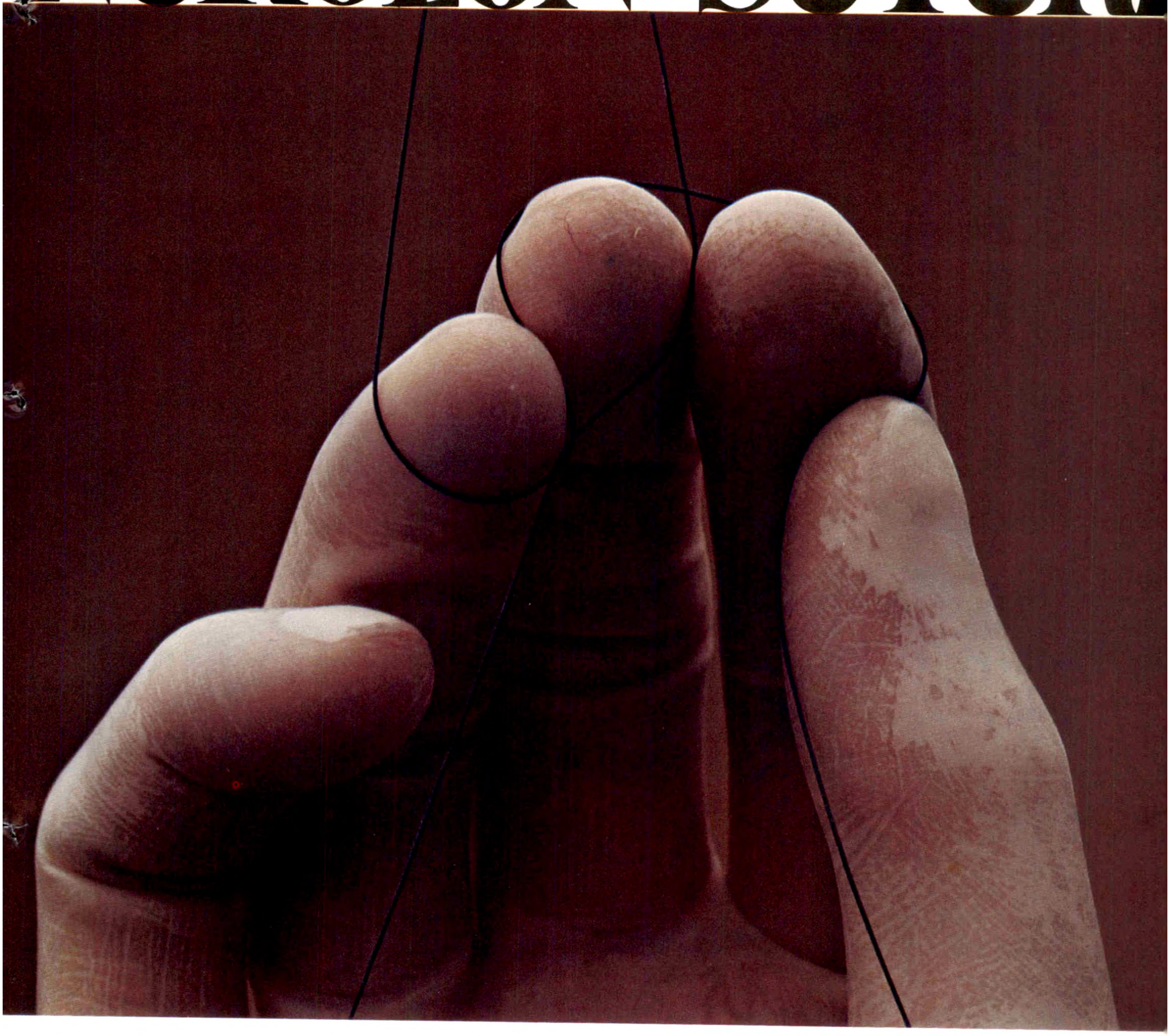

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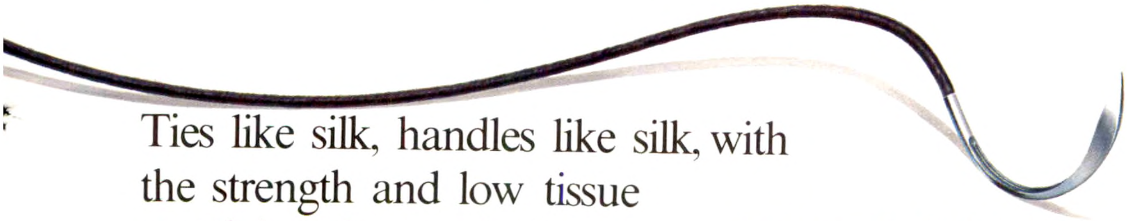

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Anaerobic GI flora–site specific

The gastrointestinal tract of man contains an abundance of microorganisms composed predominantly of anaerobic bacteria. The geographic location of these bacteria in the intestine may explain the different rates of infectious complications associated with injuries to different parts of the gastrointestinal tract. Soilage from the upper portion of the small bowel is usually associated with a lower rate of infection than from the lower small bowel and colon.

Intra-abdominal infections: Intra-abdominal infections may complicate penetrating abdominal wounds, particularly when the integrity of the bowel has been compromised. Such complications are frequently associated with trauma resulting from automobile accidents or criminal violence (such as gunshot wounds or stabbings). Anaerobic infections may occur as postsurgical complications. Peritonitis and abscess formation may cause particular problems. Intra-abdominal infections may also occur when bowel tissue becomes necrotic or nonviable as in cases of vascular compromise, embolic disease, obstruction, strangulation, toxic dilatation, and similar conditions characterized by tissue anoxia.

Appropriate therapy for the infectious complications is often a concern of many physicians.

...and how to manage them: The initiation of antibiotic therapy, particularly when peritonitis exists, may be a matter of immediate importance. In such emergency situations, the surgeon's selection of an antibiotic is frequently made on the basis of scant etiologic evidence. However, his knowledge of the specific normal flora in a given area of the bowel and how the flora can be altered by certain pathologic conditions will aid him greatly in his antibiotic selection.

Therapy which must be initiated presumptively may be chosen discriminatively: While inspection of Gram-stained specimens may prove useful, and cultures from the infection site will eventually provide valuable diagnostic information for the surgeon, the best clue to immediate antibiotic therapy may be the location of the infection. In the normal healthy adult, there is well-defined colonization by specific microorganisms in specific sites of the gastrointestinal tract. Thus a guide to the *normal* inhabitants of various areas may be helpful in suggesting the proper therapeutic agent.

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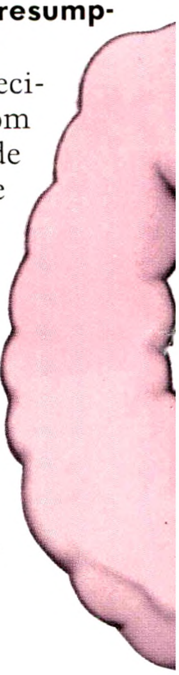
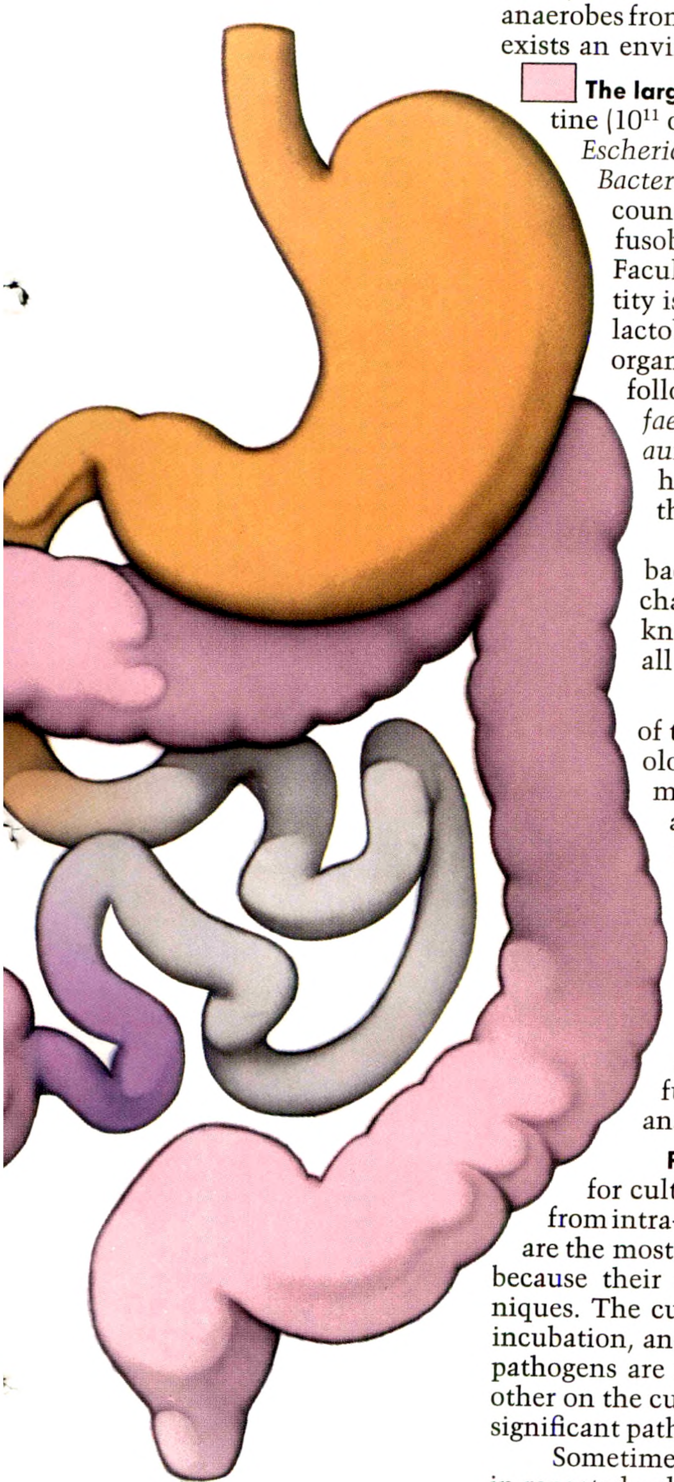


Guide to the normal adult intestinal microflora



🟧 **The stomach, and proximal and middle small bowel:** Here facultative enterococci, lactobacilli and anaerobes (originating in the oral cavity) exist in a concentration of 10^5 or less organisms per ml of contents. *Bacteroides fragilis* is virtually absent. Gastric acidity in this area limits the growth of many bacteria; therefore, most of the organisms are acid-resistant. In the middle portion of the small bowel there is sparse indigenous bacterial colonization, largely because of pronounced motility of this region.

🟪 **The distal small bowel:** In the ileum, enterococci and lactobacilli are seen in approximately the same quantities that occur in the stomach and duodenum. Coliforms are also observed—as are obligate anaerobes. *Bacteroides fragilis* and other fecal anaerobes first appear at this level. In fact, aerobic and anaerobic bacteria exist here in roughly equal proportions. The ileocecal valve, if functioning properly, provides a barrier against colonization by fecal anaerobes from the large bowel into this area. Beyond the ileocecal valve there exists an environment best suited to the proliferation of obligate anaerobes.

▢ **The large bowel:** Anaerobic microorganisms predominate the large intestine (10^{11} organisms per gram of contents). Obligate anaerobes outnumber *Escherichia coli* 1,000 to 10,000 to one in the large intestine, and *Bacteroides fragilis* is the anaerobic organism most frequently encountered. Other anaerobes, such as peptostreptococci, clostridia, fusobacteria, and eubacteria are also seen although not so profusely. Facultative aerobes are in the decided minority here, but their quantity is no less than elsewhere in the intestinal tract. Enterococci and lactobacilli are each present in concentrations of about 10^6 to 10^8 organisms per gram of contents. *Escherichia coli* is most common, followed by enterococci (*Streptococcus faecalis* and *Streptococcus faecium*), proteus, pseudomonas, and klebsiella. *Staphylococcus aureus* and *Candida albicans* are also present in the large bowel of healthy, normal individuals. The pathogenic potential of each of these microorganisms should never be overlooked.

Because the large bowel contains many different species of bacteria, disease or trauma in this area may present a special challenge. Accordingly, it is important to remember that no known single agent has proved to be uniformly effective against all of these organisms.

Variations in the normal microflora: The normal microflora of the intestinal tract may be substantially altered in certain pathological conditions. These alterations depend upon the patient's medical history and the nature of his present illness. If, for example, the patient has achlorhydria, tissue ischemia, reduced intestinal motility, blind loop syndrome or stasis, or has had previous antibiotic therapy or bowel surgery, significant changes in the microflora of the bowel may be observed. When gastric secretion, intestinal motility or anatomic integrity is altered, the flora of the small bowel may be affected. Under these conditions large numbers of facultative aerobes (e.g., *Escherichia coli*) and obligate anaerobes (*Bacteroides fragilis* and other fecal anaerobes) may be found in this area. A malfunctioning ileocecal valve could permit these aerobic and anaerobic bacteria to colonize the ileum.

Problems in diagnosis: Even though the methods currently used for culturing anaerobes have been greatly improved, bacterial cultures from intra-abdominal sites can be diagnostically misleading. Anaerobes are the most often overlooked category of potentially pathogenic organisms because their detection demands meticulous collection and culture techniques. The cultivation of certain anaerobes may require up to ten days of incubation, and even a brief exposure to air can kill many of them. Multiple pathogens are frequently encountered, and one organism can overgrow another on the culture plate. Blood cultures can be similarly deceptive, since all significant pathogens in a mixed infection are rarely isolated in a single culture.

Sometimes only the consistent reappearance of a given microorganism in repeated cultures is the clue to clinical importance.

Please turn page for information on one antibiotic of significance in the treatment of serious anaerobic intra-abdominal infections.

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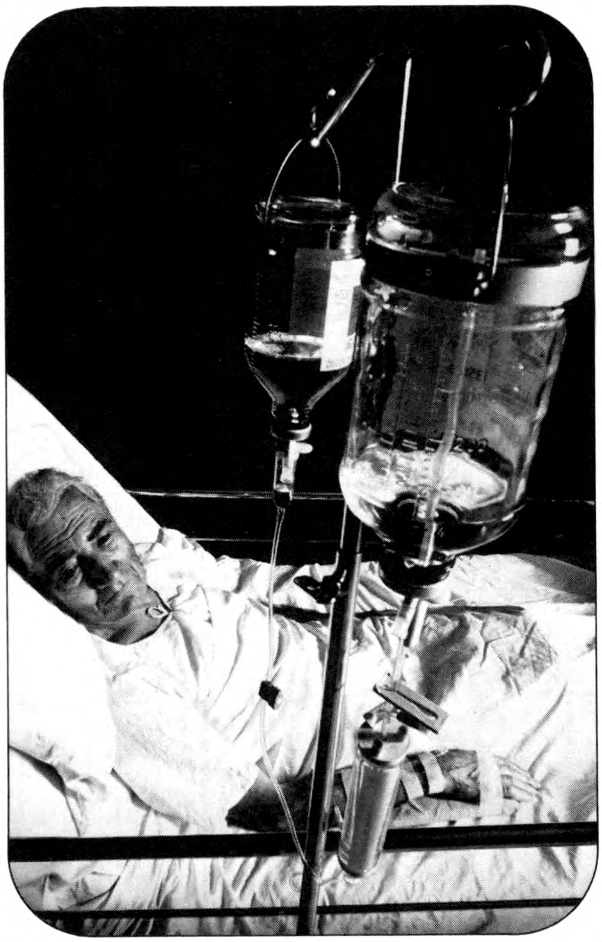
Therapeutic considerations...



Anaerobic activity: Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal-cuff infection caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Effective in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Since it is a parenteral antibiotic, Cleocin PO_4 has been evaluated in serious infections. Its use in these infections should be reserved for penicillin-allergic patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Indications include: serious lower respiratory-tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions.

Other therapeutic considerations:

1. Cleocin PO_4 is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Thus, Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section of the brief summary on the following page.

> If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

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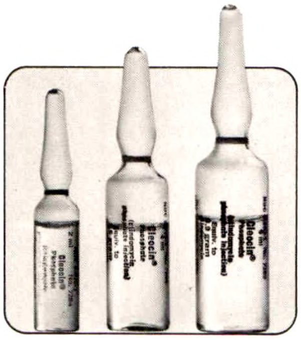
*Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g. *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION

...Cleocin® PO4

clindamycin phosphate injection, Upjohn



WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with the close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings:(See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro.* Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2, 4 and 6 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

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STERILE SOLUTION

Cleocin PO4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

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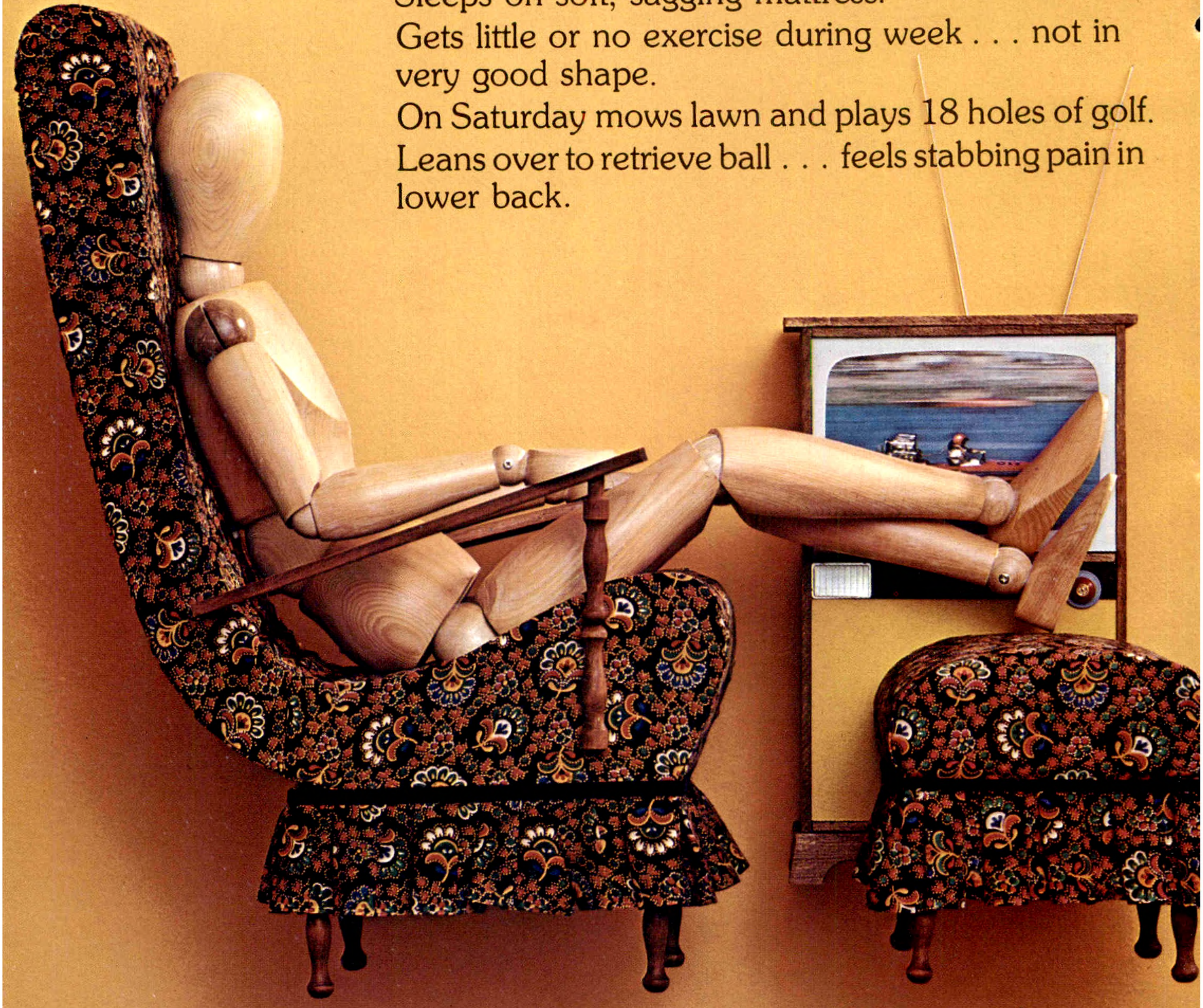
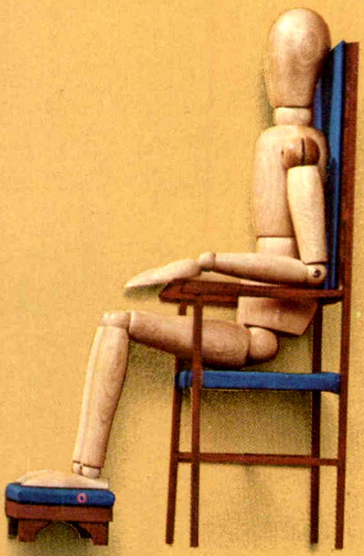
SOFT LIFE 'SUBURBANITE' BACKACHE

Sedentary job. Sits most of day in plush swivel chair.
Sits slumped in overstuffed furniture at home.
Sleeps on soft, sagging mattress.
Gets little or no exercise during week . . . not in very good shape.
On Saturday mows lawn and plays 18 holes of golf.
Leans over to retrieve ball . . . feels stabbing pain in lower back.



the solution:



At work sit in straight chair with firm back . . . knees higher than hips. Prop feet on small footstool to elevate knees. Don't sit in overstuffed furniture. Never sit long in one position . . . get up frequently and move around. Exercise regularly to strengthen abdominal and low-back muscles and help prevent weekend flare-ups. Avoid sudden spurts of vigorous physical activity. A back support can help relieve pain and fatigue.

to relieve discomforts associated with acute, painful musculoskeletal disorders...

ROBAXIN®-750

brand of

methocarbamol 750 mg. capsule-shaped tablets

the Robaxin Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood ½-¾" thick between mattress and box springs. The use of moist heat is often very beneficial.

Robaxin-750 is often indicated to relieve the discomforts associated with acute, painful musculoskeletal disorders. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.

Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:
ROBAXIN® (methocarbamol) 500 mg.

See package insert for full prescribing information.

A. H. Robins Company, Richmond, Va. 23220
A·H·ROBINS

The local that gives you the longest anesthesia gives your patient longer postoperative analgesia.

Marcaine® (Brand of bupivacaine hydrochloride) is the local anesthetic that provides the longest duration of action among commonly used local anesthetics. Which minimizes the problems during "continuous" technique or repeat doses.

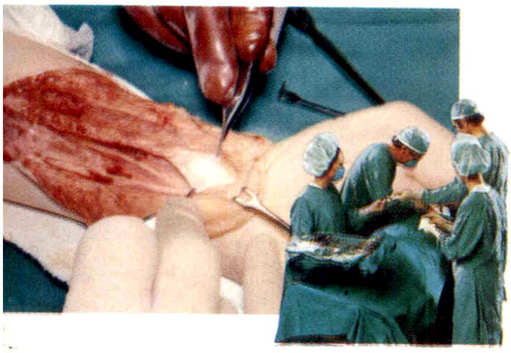
Marcaine also provides the longer postoperative analgesia. Which reduces the need for postoperative narcotics.

And in data in over 3,000 patients, Marcaine was reported to have excellent or satisfactory results in more than 96% of cases.

Extended anesthesia for the surgeon

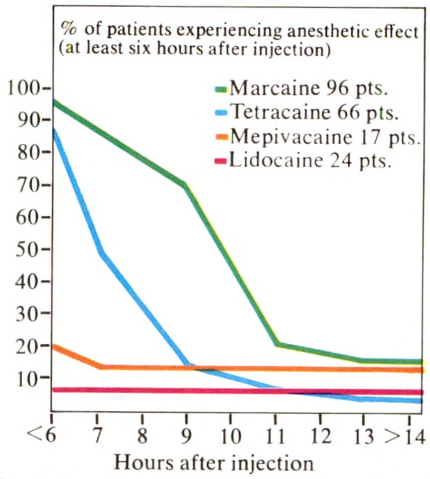
In regional blocks, Marcaine usually provides anesthesia at least 1½ to 2 times longer and occasionally even longer than lidocaine or mepivacaine. And approximately 20% longer than tetracaine. As established in several thousand surgical and obstetrical patients.[1-5]

In fact, a single Marcaine injection may be enough for up to 3½ hours of anesthesia for surgery,[5,6] and often provides analgesia that carries over into the recovery room and beyond.[8] When necessary, doses may be repeated up to once every three hours. Caution is advised in administration of repeat doses to patients with severe liver disease. Until further experience is gained, total daily dose of 400 mg. should not be exceeded nor is administration to children under 12 recommended.



This longer anesthetic action can minimize problems during "continuous" technique or repeat doses. Thus, there is the further advantage of a reduced likelihood of introducing infection since injections are less frequent.

Chart I
Duration of anesthesia
Percentage of patients experiencing anesthetic effect–
Comparison of Marcaine and other local anesthetics*



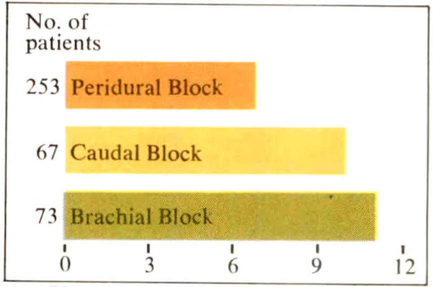
*Equipotent doses used for bilateral, simultaneous blocks of sciatic/femoral, intercostal, or brachial/axillary nerves. Adapted from Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute.

Extended postoperative analgesia for the patient

Marcaine gives your patient more—considerably more—postanesthetic analgesia than other local anesthetics in various types of nerve blocks.[3,5,8,10] An analgesia that persists after the return of sensation. As a result, you may be able to defer,[1,6] and sometimes even eliminate,[6] postoperative narcotics. The table above right illustrates the average duration of time between the initial Marcaine injection and the need for post-op analgesics.

As can be seen in Chart II, many of the 67 patients given Marcaine with epinephrine caudally for rectal surgery did not complain of pain for 12 hours or longer following induction. In another group of 40 patients[10] given Marcaine or mepivacaine locally for tonsillectomy, Marcaine pain relief lasted 3 to 5 times longer than that provided by mepivacaine. And in a study[1] of 84 patients given Marcaine caudally for perineal surgery, complete sensation returned in approximately 8½ hours for the average patient. And the majority of patients did not require a narcotic for an additional 1 to 3 hours.

Chart II
Duration of time between injection of Marcaine and need for postop analgesics†



Hours from initial injection to first hypodermic for pain

†Average—exclusion of extremes and failures. Adapted from Lund, P.C., *et al.*: *Anesth. Analg.* *49*:103, Jan.-Feb. 1970.

Excellent clinical acceptance

Marcaine was administered to 3,112 patients for various types of local anesthesia.[11] Of these patients, only 2 experienced a systemic reaction. Although Marcaine has a very wide safety margin, adverse reactions characteristic of those associated with other amide local anesthetics may occur.

Marcaine is indicated for most anesthetic blocks; however, until further clinical experience is gained, paracervical block is not recommended.

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on next page.

Extends the limits of time in anesthesia [1-5]
Extends the limits of time in postoperative analgesia [3,5,8,10]

Marcaine®

Brand of
bupivacaine hydrochloride

One local does both

Winthrop

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Actions: Parenteral administration of Marcaine stabilizes the neuronal membrane and prevents initiation and transmission of nerve impulses, thereby effecting local anesthetic action.

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies. The lowest dosage that gives effective anesthesia should be used, to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each repeated dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine (bupivacaine hydrochloride) should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation. Other causes of reactions to these local anesthetics may be hypersensitivity, idiosyncrasy, or diminished tolerance.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest.

Allergic reactions are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

In obstetrics, cases of fetal bradycardia have occurred.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium, such as ephedrine and metaraminol).

Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate or muscle relaxant, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or a short-acting muscle relaxant (succinylcholine). Intravenous muscle relaxants and barbiturates should only be administered by those familiar with their use.

References: **1.** Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine, a review of 2,077 cases, *J.A.M.A. 214*:713, Oct. 26, 1970. **2.** Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine for peripheral nerve block: a comparison with mepivacaine, lidocaine and tetracaine, *Anesthesiology 32*:460, May 1970. **3.** Hollmen, A.: Axillary plexus block: a double-blind study of 59 cases using mepivacaine and LAC-43, *Acta Anaesthesiol. Scand., Suppl. 21*:53, 1966. **4.** Herbring, B. G.: A comparative study of LAC-43, mepivacaine and tetracaine in caudal anesthesia, *Acta Anaesthesiol. Scand., Suppl. 21*:45, 1966. **5.** Bromage, P. R.: A comparison of bupivacaine and tetracaine in epidural anesthesia for surgery, *Can. Anaesth. Soc. J. 16*:37, Jan. 1969. **6.** Lund, P. C., Cwik, J. C., and Vallesteros, F.: Bupivacaine—a new long-acting local anesthetic agent, a preliminary clinical and laboratory report, *Anesth. Analg. 49*:103, Jan.-Feb. 1970. **7.** Ekblom, L. and Widman, B.: A comparison of the properties of LAC-43 prilocaine and mepivacaine in extradural anaesthesia, *Acta Anaesthesiol. Scand., Suppl. 21*:33, 1966. **8.** Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute. **9.** Wise, G. F.: Guest Discussion, *Anesth. Analg. 49*:113, Jan.-Feb. 1970. **10.** Puento-Egido, J. J., Dudeck, J., and Nolte, H.: The clinical use of the local anesthetic agent Marcaine (Carbostesin®), *Anaesthesist 16*:224, August 1967. **11.** Data in the files of the Sterling-Winthrop Research Institute.

Winthrop

Winthrop Laboratories, New York, N.Y. 10016

Extends the limits of time in anesthesia[1-5]
Extends the limits of time in postoperative analgesia[3,5,8,10]

Marcaine®
Brand of
bupivacaine hydrochloride

One local does both

(1664M)

Most Tumors are easily Recognized through the Sigmoidoscope[1]

...but you have to be able to see them, first.

Fleet® Enema helps you see them

Spiro[2] asserts that "Unless there is some contraindication, such as fulminant or bloody diarrhea, the bowel should be thoroughly cleaned before the examination."

"Many different preparations can be used," he goes on to say, "ranging from the old-fashioned saline enema to a commercially prepared phospho-soda enema . . ." and ". . . in the properly prepared bowel the entire sigmoidoscopic examination can be completed within three minutes."[2]

Gentle, thorough, thoroughly reliable FLEET ENEMA produces a clean, relaxed and mucus-free bowel in about ten minutes."[3]

- **Works rapidly, usually within 2 to 5 minutes**
- **Cleanses the left colon and rectum; spares upper portions of the GI tract**
- **Ready to use, easy to use, completely disposable**
- **Unique construction regulates flow; prevents leakage and reflux**
- **Soft, anatomically-correct prelubricated rectal tip helps avoid injury to bowel wall**

Contraindications: Do not use when nausea, vomiting, or abdominal pain is present. **Warnings:** Frequent or prolonged use of enemas may result in dependence. Take only when needed or when prescribed by a physician. **Precautions:** Do not administer to children under two years of age unless directed by a physician.

References

1. Cecil-Loeb: Textbook of Medicine, Beeson PB; McDermott W. Eds., Philadelphia, ed. 13, W. B. Saunders Co., 1971.
2. Spiro HM: Clinical Gastroenterology, The Macmillan Co., 1970.
3. Day E; Hertz RE: Booklet accompanying film, "Cancer Detection: Proctosigmoidoscopy in Office Practice," presented by C. B. Fleet Co., Inc., in cooperation with Strang Cancer Prevention Clinic Department of Preventive Medicine and Rectal-Colon Service, Department of Surgery, Memorial Hospital for Cancer and Allied Diseases, New York City, Nov., 1961.

Before sigmoidoscopy

Fleet® Enema

produces a clean, relaxed, mucus-free bowel

Fleet BRAND® pharmaceuticals

C.B. FLEET CO., INC.
Lynchburg, Va. 24505

See next page for summar
of prescribing information.

On the surgical service…

Clinical confidence earned through experience

Keflin® I.V.

sodium cephalothin

2 Gm.* in 100-ml. ampoule

The confidence that comes with 10 years' experience†

Experience with Keflin has established a record of clinical effectiveness in serious skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella.*

*Equivalent to cephalothin.

†Keflin became available for clinical investigation early in 1962 and to the profession in 1964.

Brief Summary. Consult the package literature for prescribing information.

Indications: Keflin® (sodium cephalothin, Lilly) is indicated for the treatment of serious infections caused by susceptible strains of the designated micro-organisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella*

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [020774S]

Lilly

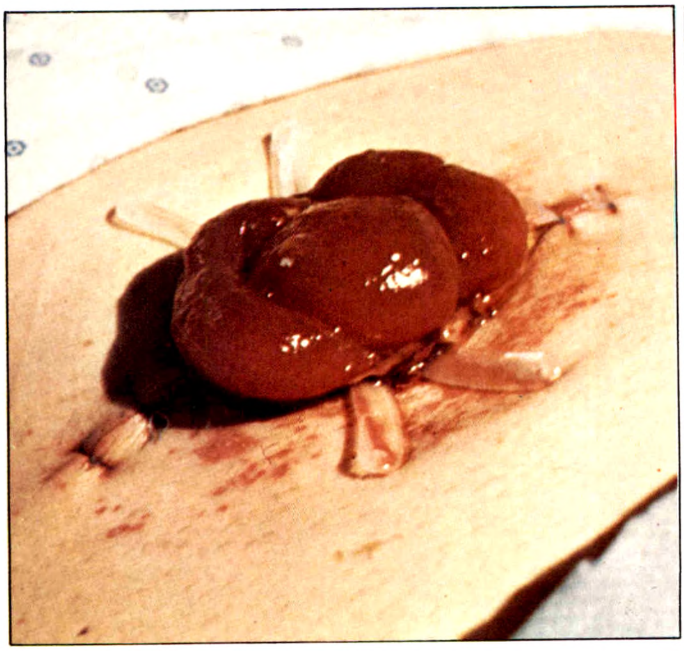
400402

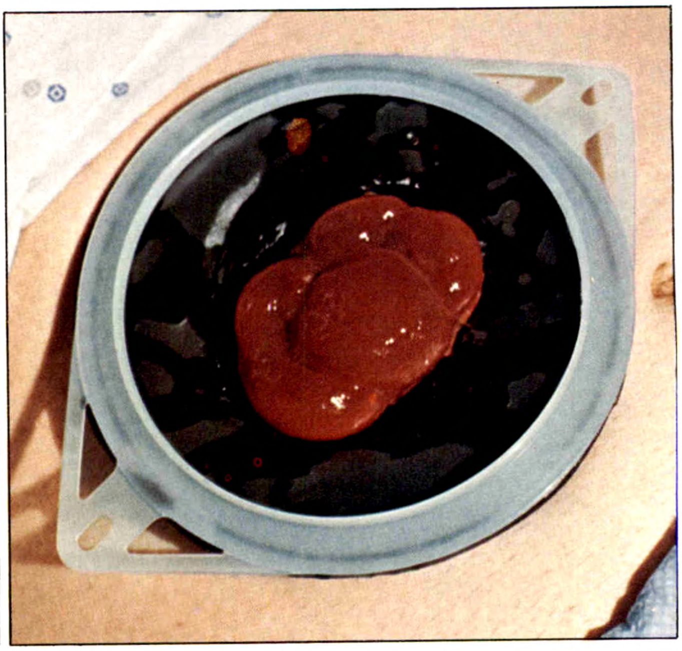
Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

for easier-to-manage loop colostomies

Using the unique Hollister Loop Ostomy Care Method instead of the traditional glass rod and rubber tubing can vastly simplify post-op management of a transverse colostomy:

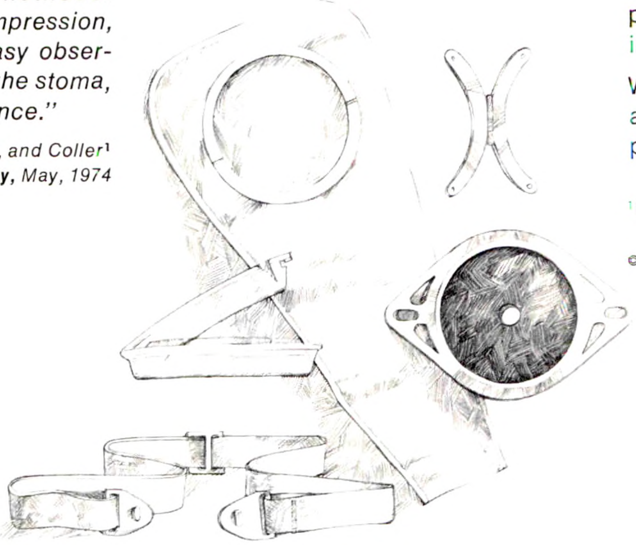




"A loop colostomy is made over a bridge so that an appliance . . . can be apposed to the skin at the end of the procedure. Experience with 40 patients has demonstrated many advantages over previous methods: immediate colonic decompression, simplified nursing care, easy observation of the circulation in the stoma, and shortened convalescence."

Corman, Veidenheimer, and Coller[1]
***Archives of Surgery**, May, 1974*

The typical rod-supported stoma is practically impossible to fit with a secure drainage appliance. Soiled bedclothes and odor are probable; skin irritation is likely.



The Hollister method uses a folding colon support that lies flat against the skin. The post-operative drainage appliance also lies flat against the skin, with a karaya gasket that fits snugly around the stoma. Skin is protected. Discharge is in the bag instead of on the patient's abdomen.

Write for professional literature and an opportunity to evaluate this simple, effective system.

[1] From the Lahey Clinic Foundation, Boston.

© 1975, HOLLISTER INCORPORATED JDS/ADV

HOLLISTER LOOP OSTOMY CARE METHOD

HOLLISTER INCORPORATED • 211 EAST CHICAGO AVENUE, CHICAGO, ILLINOIS 60611

Schering

In vitro susceptibility virtually unchanged

A five-year history of pathogen susceptibility to Garamycin (gentamicin sulfate)—1970-1974

	1970	1971	1972-73	1973-74
Gram-Negative Susceptibility No. of patient tests	97% 8,988*	97% 12,482*	97% 23,382**	97% 25,330**
Escherichia coli	96%	98%	98%	99%
Proteus species, indole-negative	97%	99%	97%	98%
Proteus species, indole-positive	98%	96%	96%	96%
Pseudomonas aeruginosa	95%	95%	94%	94%
Klebsiella-Enterobacter-Serratia	97%	98%	98%	98%
Staphylococcal Susceptibility No. of patient tests	96% 1,550*	94% 1,631*	95% 2,941**	96% 3,268**
Staphylococcus aureus	96%	95%	95%	95%
Staphylococcus, all others	97%	92%	95%	96%

Source: I.M.S. Audit of Pathology Cultures—1970-74.

These *in vitro* data are based on results obtained from hospitals in a nationwide audit. (*100 hospitals reporting; **200 hospitals reporting.) The pathogens tested were obtained from all inpatient and outpatient services.

***In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.**

See Clinical Considerations section which follows...

Garamycin®

gentamicin sulfate

injectable

40 mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

The seven major gram-negative pathogens and *Staphylococci* remain highly susceptible...

Of the seven major gram-negative pathogens encountered in the hospital, 97 per cent remained sensitive to Garamycin *in vitro* over a five-year period; 96 per cent of *Staphylococci* remained sensitive.

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin
For Parenteral Administration

> **WARNING**
>
> **Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.**
>
> **Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.**
>
> **GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.**
>
> **Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.**
>
> **In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.**
>
> **Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.**
>
> **Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.**
>
> **The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.**
>
> **USAGE IN PREGNANCY Safety for use in pregnancy has not been established.**

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lbs.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

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Ectopic Apudocarcinomas and Associated Endocrine Hyperplasias of the Foregut

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Foregut endocrine polypeptide-secreting APUD cells (Amine-Precursor-Uptake and Decarboxylation), in their embryologic migration from neural crest to foregut may become "arrested" in the mesoderm or in other ectopic locations. They may become hyperplastic, adenomatous or malignant. Eight illustrative patients are reported. One patient had "pancreatic hyperparathyroidism" with hypercalcemic crises, pancreatic apudocarcinoma, normal parathyroids, biologically active parathormone, but inert immunochemically to the usual parathyroid antisera. Two had gastrin-secreting malignancies in the mesoderm. Remission after excision, but eventual recurrence of the syndrome due to islet cell hyperplasia required total gastrectomy. One patient had a gastric corpus apudocarcinoma found prospectively with hypergastrinemia which required excision of the tumor. One patient had acromegaly with hypergastrinemia and antral gastrinosis treated by pituitary irradiation, One patient had the antral or intermediary type of the Zollinger-Ellison syndrome with moderate hypergastrinemia, duodenal ulcer and antral gastrinosis, treated by vagotomy and antrectomy. One patient had hyperparathyroidism with antral gastrinosis, treated by parathyroidectomy. One patient had malignant Zollinger-Ellison syndrome and developed associated thyroid parafollicular cell hyperplasia and parathyroid chief cell hyperplasia, treated by total gastrectomy and multiple endocrine excisions. These investigative observations demonstrate ectopic loci and associated hyperplasias which support the concept of migration and bizarre potentiality of polypeptide-secreting cells of the foregut.

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THERE ARE ENDOCRINOPATHIES, particularly in the foregut region, in which the functioning tumor is situated in an unexpected, ectopic location;[11,17,21,28,29,40,41] there are also tumors which are situated entopically, as expected, but which appear to function ectopically, i.e. by the elaboration of humoral substances which would have been expected to arise from another location.[12,13,22,30,31,40,45,48] Such observations suggest that there may be several mechanisms of development of foregut endocrine syndromes. The prevailing concept in which normally situated endocrine cells spontaneously become adenomatous or malignant and autonomously secrete their humoral substance in excess is best exemplified by insulinomas which often present a relatively "pure" syndrome. However, aberrations from that general understanding are being described for insulinomas, which include observations of mesodermal insulin-containing tumors,[5,28] hyperinsulinism due to hyperplasia without tumor,[18,19,42,44] and clinical associations suggestive of other endocrinopathies.[24] In the instance of gastrinomas a greater variability of clinical pictures emerges which raises questions as to their genesis and development (Fig. 1).[10]

In order to understand the many aberrations and the ectopic phenomena which are sometimes seen in foregut endocrinopathies of all types, including pulmonary

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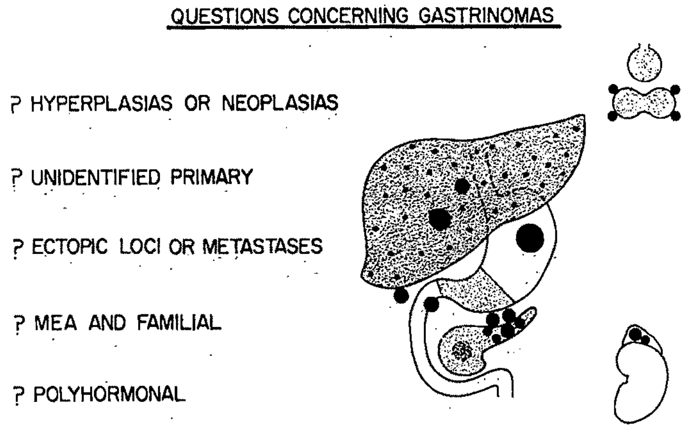
QUESTIONS CONCERNING GASTRINOMAS
? HYPERPLASIAS OR NEOPLASIAS
? UNIDENTIFIED PRIMARY
? ECTOPIC LOCI OR METASTASES
? MEA AND FAMILIAL
? POLYHORMONAL

FIG. 1. Diagram illustrating aberrations in the clinical pictures observed in the Zollinger-Ellison syndrome. Questions concerning the genesis of gastrinomas are prompted by the occasional failures to identify a primary lesion in the pancreas or to differentiate metastases from ectopic loci, or hyperplasia from neoplasia, or islet cell from carcinoid tumors; also, in comparison with insulinomas, there is a higher incidence of malignancies, of metastases, of multiple endocrine involvement, of familial associations and polyhormonal elaborations. In addition, there are unique instances of inappropriate ectopic elaboration of gastrin from parathyroid adenoma and thyroid medullary carcinoma. There are also unexplained objective observations of tumor regressions, such as the disappearance of military-type metastases in the liver and lungs.

tumors which may "inappropriately" elaborate humoral substances,[30,48] it is relevant to review briefly the embryologic and cytochemical characteristics of the endocrine secretory cells. Pearse and others have demonstrated that most of the peptide-secreting endocrine cells of the foregut have common cytochemical characteristics in which the cells take up precursor amines and decarboxylate them to form polypeptides, hence the term APUD cells (Amine Precursor Uptake, Decarboxylation).[32] The APUD series of cells appears to be one of four groups generally termed neurolophomas which by definition have their origin in the neural crest.[33] Moreover, Polak and Pearse have demonstrated experimentally the migration of these fluorogenic APUD cells from their ectodermal neural crest origin through the mesoderm to the foregut entoderm[34] where normally these cells function in homeostasis with one another. It is conceivable that arrests of such migrations in embryologic development could result in ectopic mesodermal locations of endocrine cells and subsequent tumors. The ectopic elaboration of a hormone (from an unexpected site) conceivably could occur if there had been errant migrations of cells to inappropriate sites). Also, it has been suggested that the migrating cell, being a precursor cell, may have multipotentiality for humoral elaboration.[10,48]

Ectopia thus may be the result of errors in embryologic migration and secretory potentiality. The development of hyperplasia, and neoplasia of APUD cells may not be as simply stated. Conceptually, such cellular changes may be genetically instigated, as is evident in the familial multiple endocrine adenomatosis (MEA) syndromes,[49] or hyperplasia may occur as "neo-budding" of ductile cells into islet cells,[8] or as nesidioblastosis[47] resulting in a "domino phenomenon" of successive histologic and functional changes. On the other hand, as has been suggested within the concept of nesidioblastosis, cellular hyperplasia may occur also as a secondary manifestation in response to the environment of the cells. For instance, the hypoglycemia resulting from hyperinsulinism may stimulate glucagon release and a hyperplasia of glucagon-secreting cells. The antral gastrin cell hyperplasia associated with gastric acid hypersecretory states[15,43] may be a compensatory response to the chronic acid environment which inhibits gastrin release. Antithetically, the antral G-cell hyperplasia which has been reported to be associated with pernicious anemia,[4] could be explained as an adaptive response to an environment of chronic achlorhydria in which the G-cells may be chronically stimulated. In the acid hypersecretory states (exclusive of the Zollinger-Ellison syndrome) the serum gastrin levels are within the normal range,[27] while in achlorhydric states the gastrin concentrations in the serum are usually elevated;[14,26] in any case, the release of the peptide from the cells appears to be influenced by the environment of the cells, at least until the abnormal cells secrete their hormonal substance autonomously.

Whether endocrine cell hyperplasias are the result of genetic abnormalities or of compensatory, adaptive responses to their environment in the entero-insular axis, it is relevant to use suppression and stimulation tests to determine the autonomy of the secretory capacity of the cells[3] and to differentiate, if possible, between hyperplasia and neoplasia. Progressive changes in either direction from hyperplasia to adenomatous and malignant neoplasia have not been proven.

The purpose of this report is to document some observations derived prospectively in patients which exemplify ectopic and mesodermal loci of peptide-secreting APUD cell malignancies (4 patients) and to describe examples of associated hyperplasias of APUD cells in 8 patients. These observations support concepts of embryologic errors in development of the endocrine foregut during cell migration, as well as possible environmental instigation of endocrine cell hyperplasias.

Clinical Observations

The essential manifestations observed in 8 patients are summarized in Table 1. More detailed descriptions of the pertinent clinical and laboratory studies are presented in the text for each patient and the unique features of each case are discussed in the Comments. Cases 1 through 4 illustrate ectopic locations of endocrine malignancies and ectopic sources of polypeptide elaboration and all 8 cases

TABLE 1. *Ectopic Apudocarcinomas and Associated Hyperplasias of the Endocrine Foregut.*

Patient,Age	Tumor Site	Clinical Picture	Endocrine Manifestation	Exocrine Manifestation	Associated Hyperplasia	Treatment	Comments
R.W.,8	Pancreas-liver	"Hyperparathyroidism"	? Parathormone Gastrin	Hypercalcemia	Islets Antrum	Subtotal Pancreatectomy	Death
A.T.,66	Mesodermal (Paragastric)	Zollinger-Ellison Syndrome	Gastrin	Hyperacidity	Islets Antrum	1) Excision tumors Vagotomy & antrectomy 2) Total Gastrectomy Pancreas biopsy	Well
R.L.,47	Mesodermal (parapancreatic)	Diabetes Zollinger-Ellison Syndrome	Gastrin	Hyperacidity	Islets	1) Excision tumor 2) Distal pancreatectomy 3) Total gastrectomy	Well
B.McC.,74	Antral leiomyomata Gastric fundus Apudocarcinoma	Vomiting Melena	Gastrin	Achlorhydria	Antral Gastrinosis	1) Excision antral tumors 2) Excision fundal tumor	Well
H.C.,67	Pituitary	Acromegaly	Growth Hormone Gastrin	Achlorhydria	Antral Gastrinosis	Telecobalt pituitary Irradiation	Well
R.T.,38	None	Duodenal ulcer Zollinger-Ellison Syndrome (antral type)	Gastrin	Hyperacidity	Antral Gastrinosis	Vagotomy-antrectomy	Well
J.L.,46	Parathyroid Adenoma	Hyperparathyroidism	Parathormone	Hypercalcemia Hyperacidity	Antral Gastrinosis	Excision parathyroid Adenoma	Well
L.R.,36	Adrenocortical adenoma Pancreatic apudocarcinoma (metastatic)	Cushing's syndrome Zollinger-Ellison Syndrome	Cortisol Gastrin	Hyperacidity	Islets Parathyroid Parafollicular Adrenocortical	1) Adrenalectomy 2) Total gastrectomy 3) Hypophysectomy 4) Partial parathyroidectomy	Death

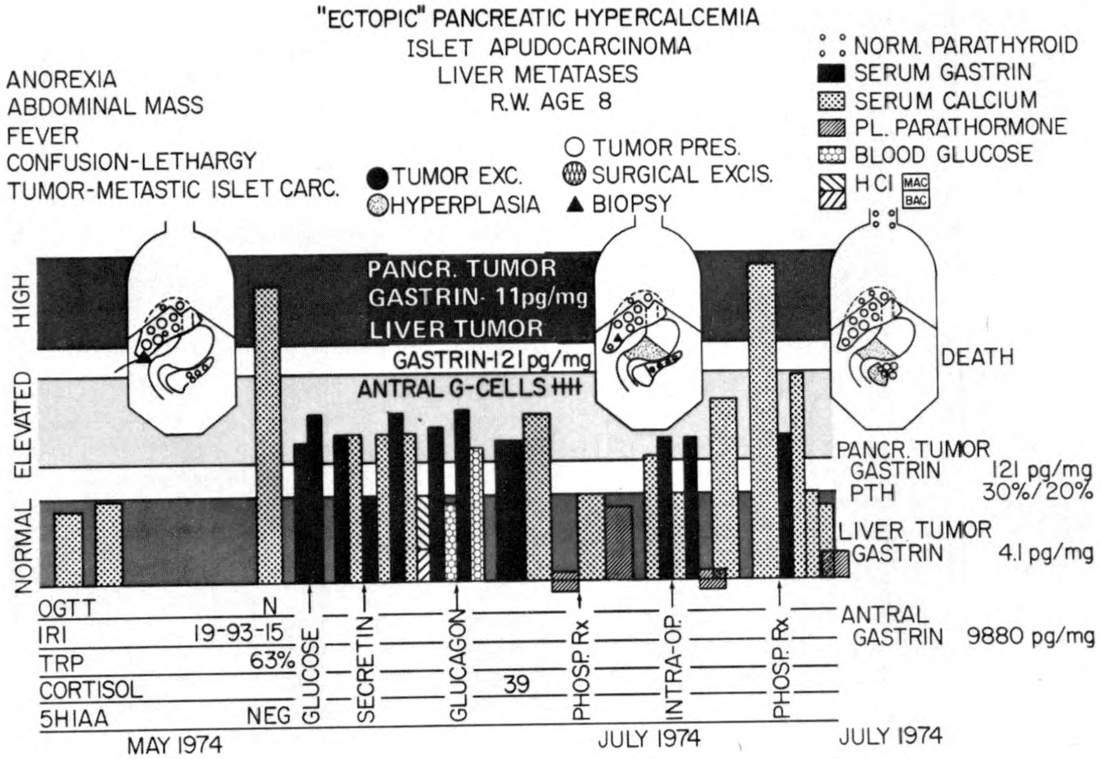

FIG. 2. Diagrammatic representation of the clinical course of patient R. W., in whom hypercalcemic crises appeared to be attributable to an ectopic source of parathormone-like activity in an apudocarcinoma of the pancreas, metastatic to the liver. The parathyroid glands were normal. The moderate elevations of serum gastrin are attributable to the antral G-cell hyperplasia.

illustrate unexpected endocrine hyperplasias which were present in association with known clinical syndromes.

Case 1. Diagnosis: "Pancreatic ectopic hyperparathyroidism"—apudocarcinoma of the pancreas with liver metastases; hypercalcemic crises associated with immunochemically inert, and suppressed levels of plasma parathormone; normal parathyroid glands, bones and kidneys; hypergastrinemia, without ulcer, associated with islet cell and antral G-cell hyperplasia.

Patient R.W. (Fig. 2) an eight-year-old boy, developed symptoms of anorexia, abdominal fullness and a low-grade fever. A palpable abdominal mass led to an exploratory operation at the patient's community hospital. A biopsy of a metastasis in the liver disclosed an islet cell carcinoma composed of APUD cells. He was transferred to the University of Kansas Medical Center where studies revealed serum calcium and phosphorus values of 14.4 and 2.9 mg%, respectively. These had been normal one week previously. Total proteins were 5.8 gm%, the total reabsorption of phosphate (TRP) ratio was 63%, and there were two determinations of undetectable levels of immunoassayable parathormone, using guinea pig antiserum to bovine parathyroid antigen. Radiologic survey of the skeletal system, as well as bone scan and bone marrow biopsy, revealed no evidence of lesions in the bones. X-rays of the chest, sella turcica, upper gastrointestinal tract and intravenous pyelography were normal; isotopic scans of the liver and pancreas were consistent with metastatic disease. A gastric analysis revealed a basal acid output (BAO) of 0.4 mEq/hr which rose to 5.3 mEq/hr on histalog stimulation; serum gastrin levels ranged between 400 and 600 pg/ml, irrespective of normal or elevated levels of serum calcium and without significant elevations when stimulated by oral glucose or intravenous secretion or glucagon. Blood glucose values were normal, with normal oral glucose tolerance. A glucagon provocative test (1 mg I.V.) produced normal peaked glucose and insulin responses. Plasma cortisol, blood serotonin levels and 5 hydroxy indole acetic acid (5HIAA) output in the urine were normal. After the hypercalcemia was corrected by means of phosphate enemas, the previously undetectable PTH, using guinea pig antibody to bovine PTH, assumed normal levels, at which time a distal subtotal pancreatectomy was done in an attempt to reduce the stimulus for hypercalcemia. Metastases in both lobes of the liver were confirmed. During operation, determinations of calcium, parathormone and gastrin levels in the venous blood from the pancreas and from the right atrium showed no significant differences in PTH or gastrin concentrations at the two loci before and after pancreatectomy. A slight but transient reduction in serum calcium occurred after resection. After 24 hours the serum calcium values gradually increased without a concomitant increase in serum gastrin values, but there was a decrease of PTH values to undetectable levels. On the fifth postoperative day, extreme weakness and obtundation associated with serum calcium values of 14 and 15 mg% necessitated treatment with phosphates with a response again to normal calcium values. The development of

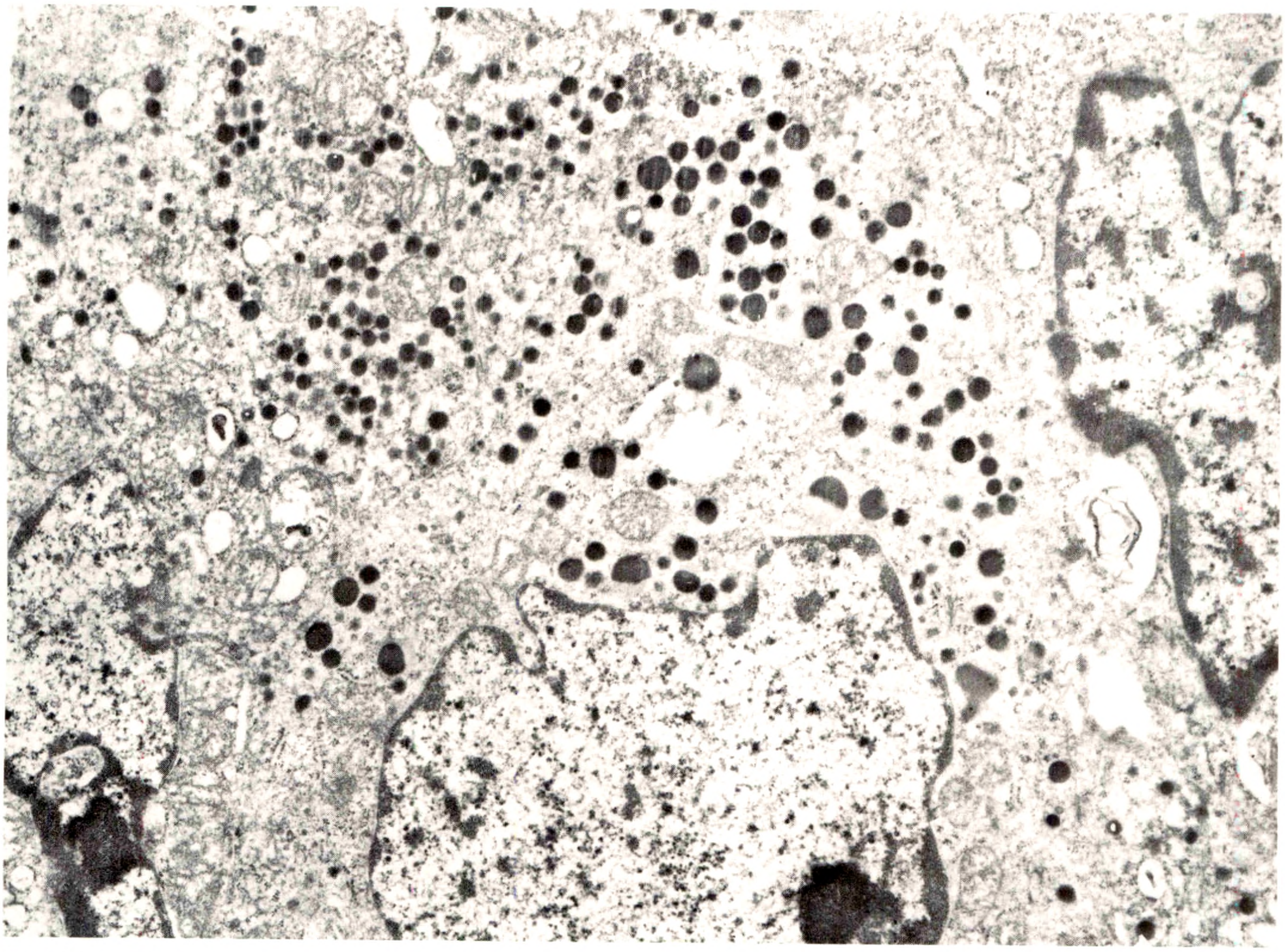

FIG. 3. Electronmicroscopic photomicrograph of portions of tumor cells from the malignant apudocarcinoma of the pancreatic islets from patient R. W. Numerous pleomorphic secretory granules are present in the cytoplasm which confirms the endocrine nature of the tumor. These granules are surrounded by a single limiting membrane and are moderately electron-dense. (Original magnification × 15,800.)

hypercalcemic nephropathy precluded the use of streptozotocin treatment. The patient developed marked ascites with ventilatory failure and died on the ninth postoperative day. At autopsy the remaining tumor was localized to the liver; the parathyroid glands were small and histologically normal; the pancreatic islets were hyperplastic; there was adrenocortical nodular hyperplasia and nephrocalcinosis; and the antral G-cells were hyperplastic (8 to 12 per acinus, the normal population is 0 to 2 cells per acinus).* Immunoassayable gastrin in the pancreatic tumor and hepatic tumor was no greater than in the hyperplastic pancreas (121 pg/mg) but the gastrin content of the antral mucosa was high (9,880 pg/mg). Immunochemical assay of the serum for PTH, during hypercalcemia, using another assay system, (guinea pig antiserum (GPI M) to porcine parathyroid antigen), yielded a just detectable value of 11 μlEq/ml of parathormone. Radioimmunoassay of the pancreatic tumor, extracted with acetic acid—acetone, using the same assay system, demonstrated nonspecific effects in the absence of antibody ("damage") with a 10% increment increase of free parathormone over bound parathormone. Immunofluorescent studies, using antiserum G.P. 012, did not demonstrate cellular localization of immunoreactive PTH in the tumor. These results are interpreted to indicate that the PTH molecule from ectopic sources may in some way be aberrant, such that it is not recognized by any of the antisera used in these studies. Electronmicroscopy of the pancreatic and hepatic tumor cells, however, revealed abundant secretory granules, confirming the endocrine nature of the tumor (Fig. 3). The granules are strikingly different from alpha, beta or delta cell granules of the islets of Langerhans. The

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*Antral mucosal biopsy specimens were prepared for light microscopy by toluidine blue staining of glutaraldehyde-fixed, resin-imbedded sections. It is cautioned that the G-cell population estimations are gross counts of cells located specifically in the juncture of the middle and deep thirds of the antral mucosa, which have the morphologic appearance of G-cells (large, round, oval, "clear" cells with a large nucleus) and which can be further identified by immunofluorescence as gastrin cells. For more accurate quantitation, more specific preparations are advisable.[25]

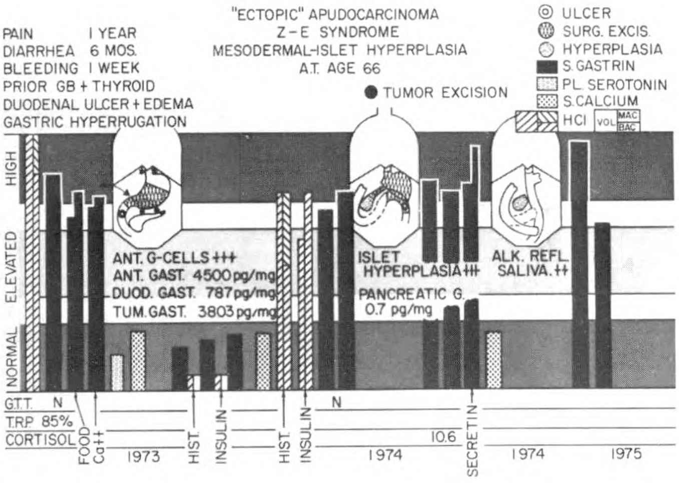

FIG. 4. Diagrammatic representation of the clinical course of patient A. T., in whom excision of two ectopic mesodermal gastrin-secreting "apudocarcinomas" plus antrectomy, only temporarily altered the course of the Zollinger-Ellison syndrome. The redevelopment of acid hypersecretion, hypergastrinemia and stomal ulceration secondary to islet cell hyperplasia required total gastrectomy. The elevated serum gastrin is decreasing.

possibility that this tumor may have arisen from a "fourth cell type" is likely.

Comment: The clinical findings in this patient suggest an ectopic locus for an unidentified parathormone-like substance from the apudocarcinoma of the pancreatic islets and the liver tumor. The hypercalcemia, hypophosphatemia and reduced tubular reabsorption of phosphate are consistent with other reported examples of ectopic elaboration of a PTH-like substance.[1,7,23,30,31,37,39] The identification of secretory granules in this case distinguishes this tumor from non-endocrine malignances with hypercalcemia (pseudohyperparathyroidism).[1,16] The immunochemical studies of the sera and tumor, and the immunofluorescent studies of the tumor indicate that the aberrant PTH-like molecule is of different antigenicity than the parathormones elaborated by parathyroid glands.[2,31] It is possible that the hypercalcemic agent is yet another substance, such as a prostaglandin.[38] It is less likely that the parathyroid glands are the source of the humoral substance because of their small, histologically normal appearance, and the lack of higher levels of plasma PTH in the jugular veins than in the pancreatic-portal veins. Furthermore, secondary parathyroid gland secretion of PTH which could be stimulated by glucagon elaboration from the tumor is unlikely in this patient because there was no fasting hyperglycemia, and there were normal glucose and insulin responses to both oral glucose and intravenous glucagon. It is interesting to note that the serum calcium and PTH levels in this patient correlated inversely, which suggests that the hypercalcemia suppressed the PTH elaboration from his own normal parathyroid glands. It is reasonable to assume that the moderate hypergastrinemia without ulcerogenic consequences may have resulted from antral G-cell hyperplasia, rather than as a consequence of pancreatic elaboration of gastrin. Endocrine screening of this patient's family has yielded a paternal grandfather with sellar enlargement consistent with a benign pituitary adenoma, and a father with gastric acid hypersecretion.

Case 2. Diagnosis: Two ectopic mesodermal malignant paragastric gastrinomas, antral G-cell hyperplasia; Zollinger-Ellison syndrome with remission after excision of the tumors and the antrum, but subsequent recurrence due to ulcerogenic islet cell hyperplasia which required total gastrectomy.

Patient A.T., (Fig. 4), a 66-year-old woman, related a one-year history of upper abdominal pain, initially relieved by food intake. She developed diarrhea 6 months prior to study and had two episodes of "tarry stools." An upper gastrointestinal x-ray series demonstrated a duodenal ulcer, duodenal spiculation and jejunal flocculation. A celiac angiogram demonstrated no tumor blush and liver scan was normal. Gastric acid secretory studies revealed a 12-hour overnight volume of 4510 ml; basal acid secretion was 370 mEq/12 hr. Repeat studies showed a basal acid output of 20 mEq/hr which on histalog stimulation increased to 38 mEq/hr, a ratio of 0.5. Serum gastrin determination by immunochemical assay was 2850 pg/ml; additional values ranged between 768 and 1200 pg/ml. Feeding and intravenous infusion of calcium (5 mg/Kg/hr) produced only a 10% increase in serum gastrin values. Serotonin and parathormone assays of plasma were within normal range. A 2-hour postprandial blood glucose was at the upper limit of normal (116 mg%), 5HIAA in the urine was qualitatively negative, and the TRP ratio was 85%. An antral mucosal biopsy at endoscopy revealed moderate hyperplasia of G-cells (2 to 5 G-cells per mucous acinus). With a diagnosis of Zollinger-Ellison syndrome, an operation revealed a duodenal ulcer, a grossly and microscopically normal-appearing pancreas, no tumor of the duodenum, no evidence of metastatic disease in lymph nodes or liver, and a thickened stomach without tumor; on close inspection, however, two soft nodules, approximately 6 x 15 mm each, were found in peritoneal planes of the lesser omental sac adjacent and posterior to the stomach (Fig. 5). Frozen and permanent sections of these excised nodules were reported as APUD cell tumors, having malignant endocrine characteristics consistent with islet cell tumors. There was a lack of argentophilia and no evidence of lymph nodal tissue. It was thought, based on prior experience, that excision of the two mesodermal "rests" might not control the hypergastrinemia and, because of the known antral G-cell hyperplasia, an antrectomy with vagotomy was added to the operative treatment. Postoperatively the acid secretory patterns revealed no acid basally, after either stimulation by histolog

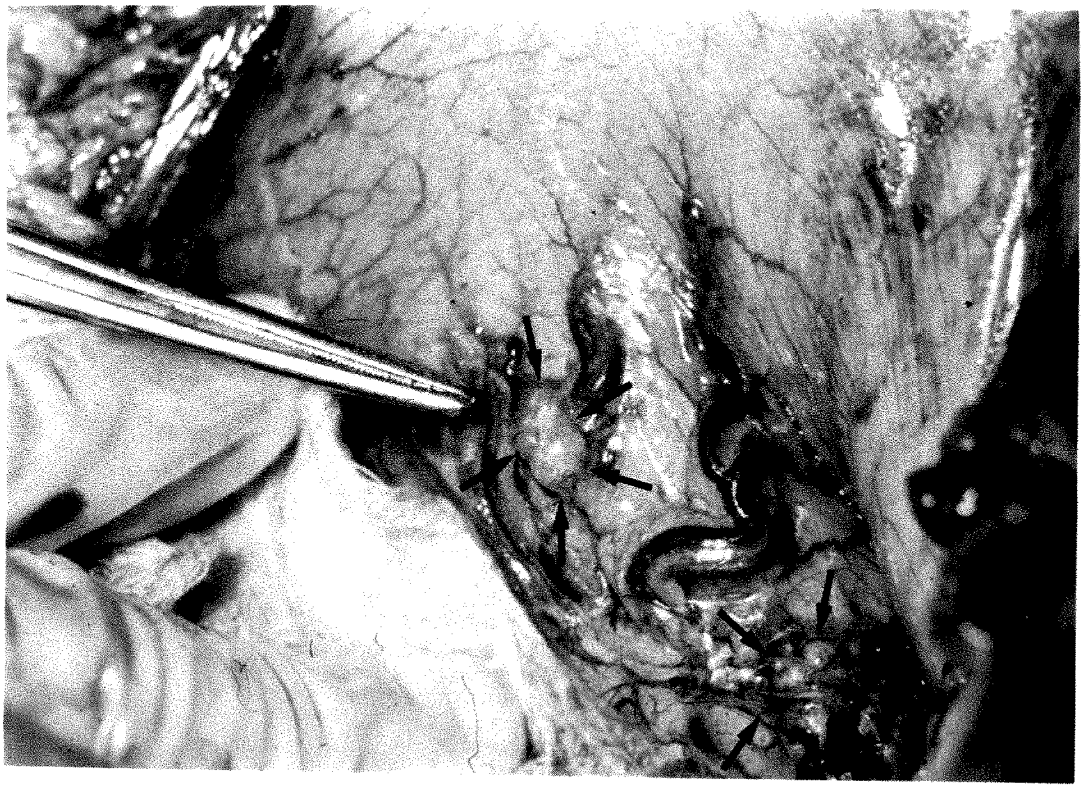

FIG. 5. Photograph taken during operative exploration of patient A. T., which illustrates two ectopic, mesodermal, retrogastric nodules (marked by arrows) in the lesser omental sac. These nodules, which were devoid of any lymph node characteristics histologically, contained gastrin (3800 pg/mg) by immunochemical assay.

or after insulin hypoglycemia. Serum gastrin values fell to 181, 209, and 253 pg/ml immediately. The mesodermal tumors contained gastrin (3800 pg/mg) comparable to that in the antral mucosa (4500 pg/mg) as determined by immunochemical assay. The patient was asymptomatic for a period of 4 months, after which she developed pain in the left upper abdomen which radiated to the back. She also described the onset of watery bowel movements. Upper gastrointestinal x-ray examination demonstrated two large stomal ulcers at the gastrojejunostomy. A 12-hour gastric volume now was 1600 ml, containing 126 mEq/12 hr. The ratio of the basal acid output to maximal acid output on histalog stimulation was 0.6. A Hollander test which produced an hypoglycemia of 35 mg%, stimulated acid secretion from 68 mEq/L basally to 118 mEq/L. The serum gastrin values were elevated to levels between 800 and 1000 pg/ml.

With a diagnosis of recurrent Zollinger-Ellison syndrome, thorough exploration at operation disclosed stomal ulceration but no further tumors or evidence of metastases. A distal (5 cm) amputation of the tail of the pancreas revealed an increase in the size and number of islets on frozen section. (Permanent sections revealed islet cell hyperplasia with evidence of nesidioblastosis.) Based on the clinical findings of stomal ulcer, recurrent acid hypersecretion, elevated serum gastrin values, and islet cell hyperplasia on frozen section, a total gastrectomy was done. The pancreas contained very little gastrin (0.7 pg/mg). The abdominal pain disappeared but the patient began to experience "heart burn," and "excessive" salivation (apparent but not quantitatively increased) and the serum gastrin two months postgastrectomy was over 1000 pg/ml, rising to 1400 pg/ml in three months and to 1900 pg/ml in five months. Mechanical dilatation of the esophagojejunostomy failed to relieve the "alkaline reflux and salivation." Secretin (96 Jorpes units I.V.) stimulation slightly elevated the serum gastrin levels (1962 pg/ml base to 2333 pg/ml at one hour) without alterations in calcium, glucose, immunoreactive insulin or human growth hormone levels. Surgical revision of the Roux en Y from a 14 inch to a 30 inch limb failed to effect relief of the patient's symptoms. At the present time, 9 months after total gastrectomy, the symptoms are spontaneously relenting and the serum gastrin content is decreasing (946 pg/ml). The submaxillary salivary glands have been prominent, but not enlarged.

Comment: This patient illustrates the Zollinger-Ellison syndrome which can be associated with ectopic mesodermal APUD cell tumors, containing gastrin by immunochemical assay. Temporary remission of symptoms, acid values, and serum gastrin values occurred after excision of these tumors, together with antrectomy and vagotomy (because of the associated antral G-cell hyperplasia). Recurrence of symptoms due to stomal ulceration after 4 months, with recrudescence of acid hypersecretion and increased serum gastrin values required total gastrectomy, at which time the only APUD cell abnormality which could be found was islet cell

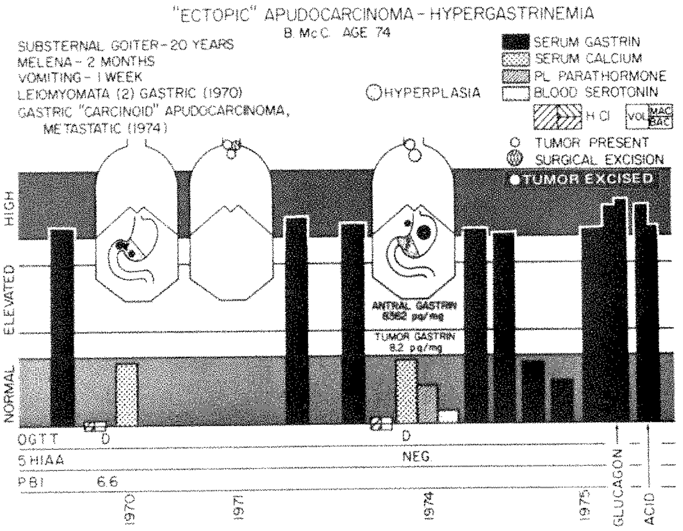

FIG. 6. Diagrammatic representation of the clinical course of patient B. McC., in whom a malignant, ectopic apudocarcinoma of the body of the stomach developed 4 years after excision of two leiomyomata of the antrum, during prospective studies of her hypergastrinemia, achlorhydria, antral gastrinosis and diabetes melitus.

hyperplasia. Protracted elevations of serum gastrin levels with symptoms of reflux and salivation call to mind a report of salivary gland and duodenal Brunner's gland hyperplasia in a Zollinger-Ellison patient.[20] It remains to be seen whether further difficulties relative to her islet cell hyperplasia or other potential tumors will occur in the future.

Case 3. Diagnosis: Ectopic mesodermal malignant parapancreatic gastrinoma, with persistence of the Zollinger-Ellison syndrome after excision of the tumor and the distal pancreas; associated ulcerogenic islet cell hyperplasia which eventually required total gastrectomy; amelioration of the diabetes mellitus. (This case has been reported in part previously[12] but is included here to illustrate the mesodermal nature of the tumor, a fact not fully appreciated, except in retrospective study.)

R. L., a 47-year-old man with longstanding diabetes mellitus, was operated upon for an umbilical hernia, during which operation a mass anterior to the pancreas was palpated and removed. The parapancreatic tumor proved to be malignant histologically. A subsequent distal pancreatectomy and a second-look procedure failed to demonstrate persistent neoplasia (only islet cell hyperplasia was found); these procedures did not alleviate the progressive nature of the ulcerogenic syndrome. A total gastrectomy eliminated the syndrome and significantly reduced the patient's insulin requirements. At the present time, 8 years after total gastrectomy, the patient is clinically well with normal serum gastrin values but is requiring insulin treatment again. There is intolerance to oral glucose; also there is a relatively flat response of glucose levels to exogenous glucagon (1 mg I.V.) (glucose levels rising from 312 mg% to 339 mg% in 15 minutes). Levels of immunoreactive insulin have been unmeasurable because of the excessively high circulating insulin antibodies. Assays for glucagon have not been done. At the present time the determinations of calcium, parathormone, serotonin, human growth hormone are normal, as are serum gastrin values.

Comment: Upon review of the operative findings and of the histology of the parapancreatic islet cell carcinoma, it is apparent now that the tumor was not situated in pancreatic or lymph node tissues; for these reasons an ectopic mesodermal locus is ascribed to it. The associated islet hyperplasia proved to be progressively ulcerogenic. It is interesting to note that one of the two patients in the original report of the syndrome by Zollinger and Ellison demonstrated two nodules, one "islet cell tumor on the surface of the pancreas, with metastases in an adjacent lymph node."[50] The development of

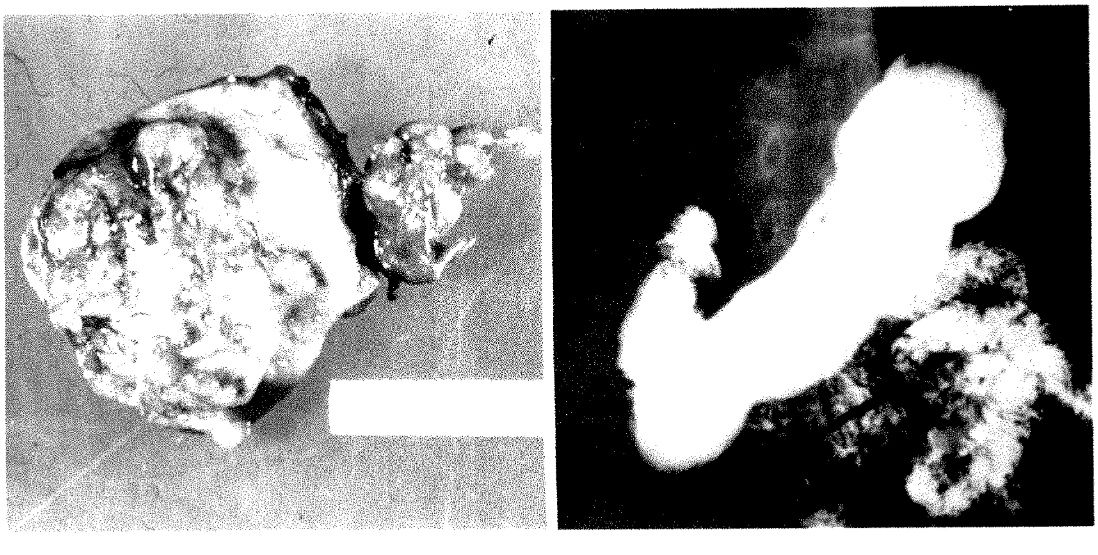

FIG. 7. Photograph (left) of the ulcerating apudocarcinoma and lymph node metastases which were removed from the gastric corpus in patient B. McC. The ectopic location high on the lesser curvature is seen on the x-ray on the right.

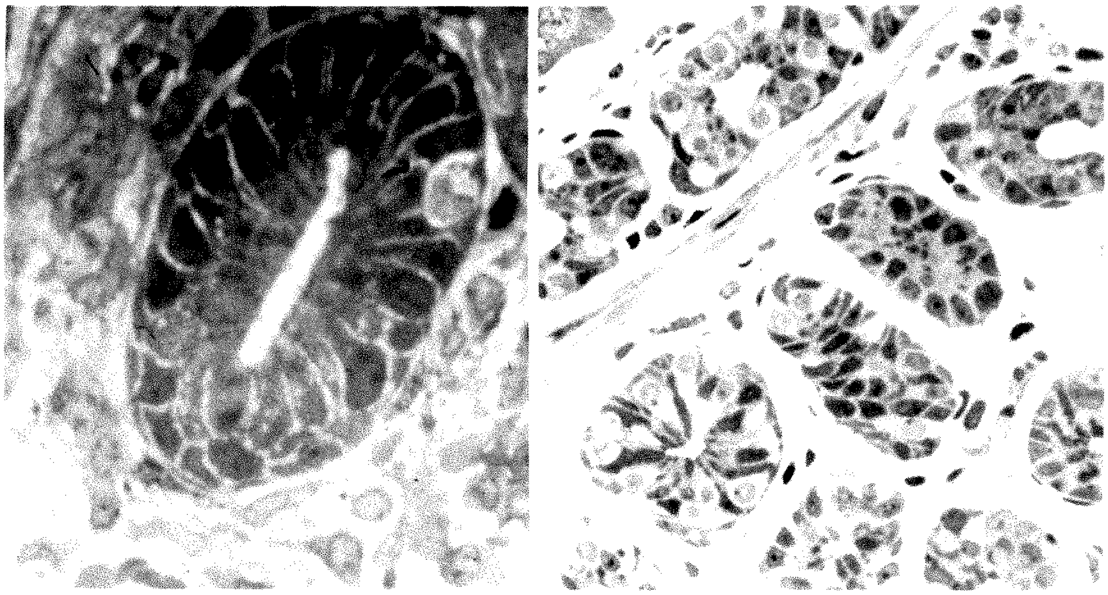

FIG. 8. Photomicrographs illustrating, on the right the increased antral G-cell population (8-12/acinus) (clear, round, oval cells) in patient H. C., as compared to the normal (0-2 cells/acinus) picture seen on the left. The antral G-cell hyperplasia in this patient is associated with achlorhydria, without anemia, hypergastrinemia, and acromegaly. (Original magnification ×480 and ×440.)

the syndrome in R. L., superimposed on diabetes mellitus with amelioration of the insulin requirements after total gastrectomy, and the more recent return to a diabetic picture, only mildly responsive to exogenous glucagon, all suggest that environmental influences may affect polypeptide homeostasis within the entero-insular axis.[46]

Case 4. Diagnosis: Ectopic apudocarcinoma located in the body of the stomach which was found prospectively in a patient with hypergastrinemia, antral gastrinosis, achlorhydria without anemia, and diabetes mellitus.

B. McC., (Fig. 6), a 74-year-old woman with diabetes mellitus, gave a history of a "goiter" which had been present for 20 years. Two months prior to her first hospital admission there was an episode of melena and vomiting of one week's duration. Appropriate studies demonstrated pedunculated tumors of the antrum with prolapse into the duodenal lumen, achlorhydria to histamine, and cholecystolithiasis; an excision of two leiomyomata of the antrum, a cholecystectomy and an incidental appendectomy were performed in 1970 without sequellae. A serum gastrin determination obtained during that hospitalization was reported as 1110 pg/ml; this was confirmed on several occasions and was considered to be compatible with histamine-fast achlorhydria. In 1971 a partial thyroidectomy for colloid goiter was done in a hospital in her community. In 1974 the patient complained of chest pain, belching and vomiting of one week's duration. Upper gastrointestinal x-rays demonstrated a large ulcer crater located high on the posterior wall of the stomach, having the appearance of malignancy (Fig. 7). There was continued achlorhydria to histalog stimulation; serum gastrin determinations ranged from 1103 to 1292 pg/ml. Other laboratory determinations were within normal limits, including a blood serotonin level. At operation a large, localized, ulcerated apudocarcinoma having some cytologic characteristics of a carcinoid tumor, with lymph node metastases, was excised; the liver appeared normal. The tumor contained a very small amount of gastrin by immunochemical assay (8.2 and 10.4 pg/mg); the antral mucosa, however, contained 8360 pg/mg. There was hyperplasia of the G-cells in the antrum (6 to 10/acinus); no gastrin cells and very few parietal cells were discernible histologically in the mucosa of the body of the stomach. By 15 days after operation the serum gastrin level decreased to normal levels of 68 and 125 pg/ml. Re-evaluation 3 months later disclosed that the serum gastrin levels were again elevated to levels of 1008 to 2386 pg/ml; there was persistent achlorhydria and the G-cell population of the antral mucosa was still increased. Intragastric administration of 0.1 N hydrochloric acid (pH = 1.6) over a period of 60 minutes (120 drops/min) produced a slight decrease in serum gastrin levels from 2341 to 1752 pg/ml over 75 minutes. An isotopic scan of the liver was compatible with a diagnosis of hepatic metastases; a needle biopsy did not confirm that diagnosis. The patient is being prospectively observed.

Comment: It seems reasonable to assume that the ectopic APUD cell malignancy of the body of the stomach is related in some unknown way to the hypergastrinemia, achlorhydria and antral G-cell hyperplasia, each of which apparently preceded the development of the metastasizing tumor. Although gastrin-containing tumors of the stomach have been reported previously,[17,21,41] the development of one in the non-antral portion of the stomach while under observation of hypergastrinemia has not been described previously. The failure of intra-gastric acidification to significantly suppress serum gastrin levels suggests that the probable metastatic apudocarcinoma in the liver autonomously releases gastrin and that the re-

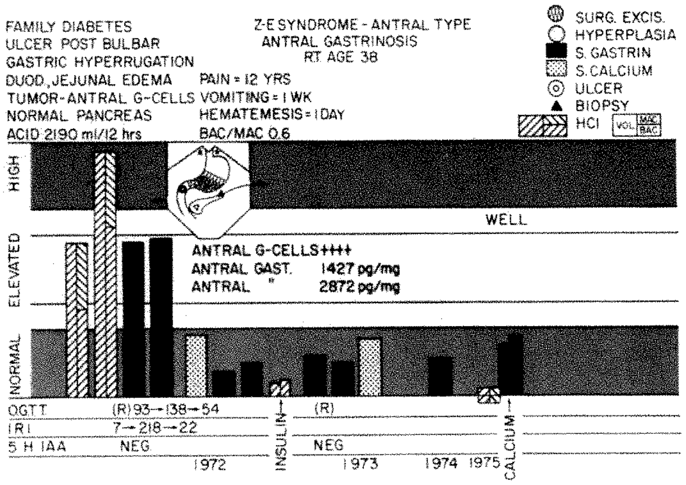

FIG 9. Diagrammatic representation of the clinical course of patient R. T. in whom the clinical findings suggested the diagnosis of the Zollinger-Ellison syndrome. The moderate elevation of the serum gastrin (400-1000 pg/ml), however, was attributable to antral G-cell hyperplasia without other APUD cell abnormalities. An antrectomy with vagotomy promptly reversed the antral or intermediary type of the "Zollinger-Ellison" syndrome.

current hypergastrinemia is not secondary to antral release of gastrin.

Case 5. Diagnosis: Pituitary acromegaly, elevated human growth hormone levels with associated antral G-cell hyperplasia, hypergastrinemia, and histamine-fast achlorhydria, treated by telecobalt irradiation of the pituitary.

H. C., a 67-year-old woman, first noted enlarging hands and feet 15 years prior to these studies; for one year she had also noted abdominal cramping pains, occasional melena, fatigue and polyuria with polydipsia. Physical examination demonstrated prognathism, macroglossia, prominent orbits and frontal bossing, enlarged hands and feet, and moderate hypertension (180/100 mm Hg). Human growth hormone values were elevated 28 to 49 ng/ml during an oral glucose tolerance test with diabetic glucose intolerance and persistently moderately elevated levels of serum gastrin between 400 and 500 pg/ml. Gastric aspiration yielded 215 ml in 12 hours with a pH of 7.1 and an achlorhydria refractory to histalog stimulation. The level of vitamin B_{12} in the blood was normal (546 pg/ml) and serum parietal cell antibodies were present. The patient was treated by telecobalt irradiation (4608 r/3 weeks). In 6 months, during re-evaluation, there was symptomatic improvement and diminution of growth hormone levels to 18 ng/ml. At 9 months following treatment the growth hormone levels returned to their high levels and the serum gastrin values increased to 1104 pg/ml fasting, with no increased response to intravenous exogenous glucagon (1 mg). There were normal, peaked glucose and insulin responses to glucagon. The patient was still achlorhydric without anemia and the G-cell population of the antral mucosa was increased, (8 to 12/acinus), indicative of G-cell hyperplasia (Fig. 8).

Comment: This patient illustrates a combination of findings which are probably interrelated, though a cause and effect relationship is not evident at this time. Acromegaly, antral gastrinosis and hypergastrinemia in this patient are associated with gastric achlorhydria, rather than with acid hypersecretion, as has been reported previously.[4,43] Hypergastrinemia has been reported in association with achlorhydria with and without pernicious anemia and has been shown to decrease significantly during intragastric administration of 0.1 N hydrochloric acid.[14] The increased levels of serum gastrin after irradiation therapy to the pituitary gland in this patient have not been explained, but may be related to the G-cell hyperplasia in the antral mucosa.

Case 6. Diagnosis: Duodenal ulcer, postbulbar, Zollinger-Ellison syndrome (antral type); gastric hyperacidity; moderate hypergastrinemia associated with antral gastrinosis and normal pancreatic islets, treated satisfactorily by antrectomy and vagotomy.

R. T. (Fig. 9), a 38-year-old man, presented a history of abdominal pain of 12 years' duration with radiologically documented duodenal ulcer for 10 years. Increasing severity of the ulcer pain culminated in vomiting and hematemesis in spite of regulated out-patient medical management. X-ray examinations demonstrated, in addition to a post-bulbar ulceration, prominent duodenal folds, gastric hyperrugation, jejunal edema and a non-visualized gall bladder after double dosage. Endoscopy confirmed the ulceration. Gastric analysis demonstrated an overnight 12-hour volume of 2190 ml with an increase in basal acid output from 15 mEq/hr to 43 mEq/hr after histalog stimulation. The serum gastrin concentration was 558 pg/ml. The G-cell population of the antral mucosa was hyperplastic (10 to 12 G-cells/acinus). Calcium levels were normal. An oral glucose tolerance test showed only mild glucose intolerance but there was a marked insulin response to the hyperglycemia (from 7 to 218 μU/ml when the blood sugar was 238 mg%). At operation no islet cell abnormalities could be found histologically in the biopsies of the tail and head of the pancreas, or in adjacent lymph nodes or the duodenum. Accordingly, truncal vagotomy and antrectomy were done. There was an immediate resolution of the elevated serum gastrin levels to 126 pg/ml after vagotomy and to 67 pg/ml after antrectomy. During operation, but prior to vagotomy and antrectomy, a bicarbonate solution was instilled intragastrically (200 ml at pH 8.0) with little change in serum gastrin levels (from 430 to 480 pg/ml); the antral mucosal gastrin content decreased from 1427 to 1021 pg/ml. Postoperatively the insulin gastric analysis demonstrated no increase in a basal gastric acid concentration of 11 mEq/L during hypoglycemia of 27 mg%. A

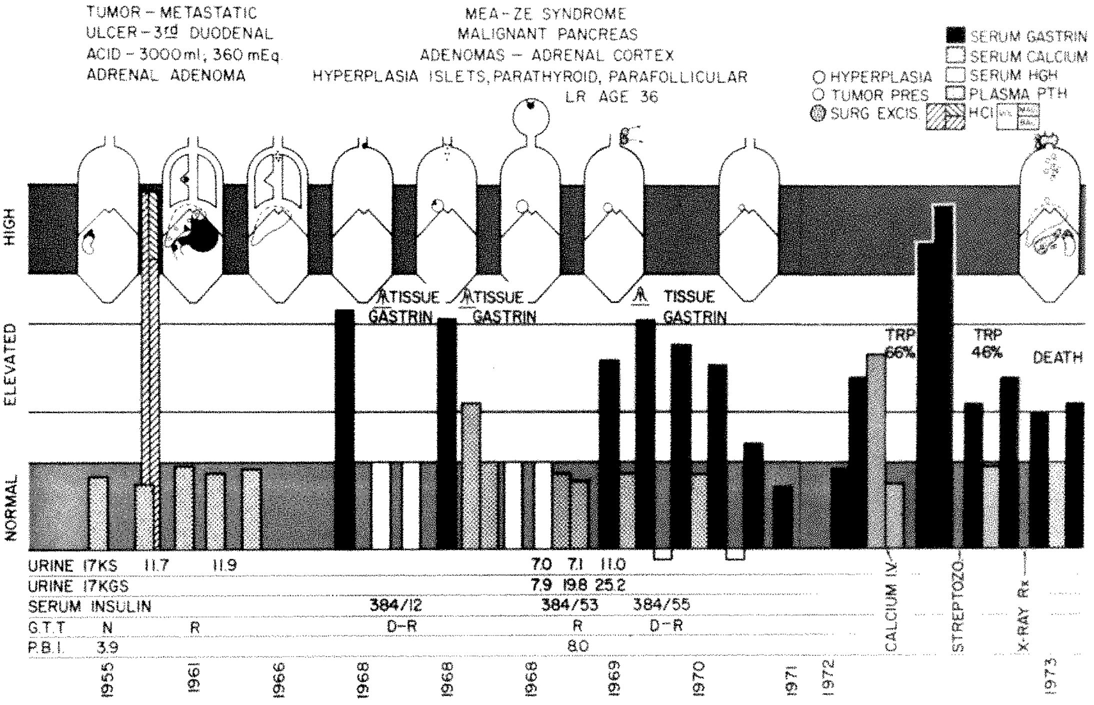

FIG. 10. Diagrammatic representation of the clinical course of patient L.R. in whom multiple endocrine adenomatosis ranged from APUD cell hyperplasias to benign and malignant APUD cell neoplasias. There were two significant periods of ulcerogenic tumor regression (7 years after total gastrectomy, and 5 years after hypophysectomy). Death 18 years after right adrenalectomy was relatively precipitous and was associated with cellular hyperplasia of the two remaining parathyroid glands, the thyroid parafollicular cells, the opposite adrenal cortex, and the pancreatic islets.

three-year follow-up revealed normal fasting gastrin levels in the serum, with a response from 95 to 209 pg/ml on induced hypercalcemia. There was basal gastric achlorhydria with no acid response to insulin hypoglycemia or histalog administration, and there was no evidence of recurrent ulcer nor endocrinopathies.

Comment: The clinical and radiologic findings which are strongly suggestive of the Zollinger-Ellison syndrome, but which are accompanied by only moderate elevations of serum gastrin levels (400 to 1000 pg/ml) deserve careful scrutiny. If, as shown in this patient, there is antral G-cell hyperplasia, without pancreatic islet cell or duodenal mucosal abnormalities, an antrectomy with vagotomy should suffice as adequate treatment and should be clearly confirmed by observing the reduced gastric acid secretion in the postoperative course. Polak et al. have described a Zollinger-Ellison syndrome, type I, with antral gastrinoma,[35] as being differentiated from the original type described by Zollinger and Ellison based primarily on an antral rather than a pancreatic source of gastrin elaboration. It has also been postulated that the antral variety described here may represent a transitional stage or intermediate type between the duodenal ulcer diathesis and the classical pancreatic islet cell ulcerogenic syndrome.[13] A "borderline ulcerogenic tumor syndrome" has also been described by Zollinger which has not been attributed to antral dysfunction.[51] It is possible that other gastrin cell tumors of the antrum reported previously probably represent a further stage of evolution from hyperplasia to neoplasia.

Case 7. Diagnosis: Non-familial parathyroid adenoma with hyperparathyroidism associated with antral gastrinosis, gastric hyperacidity and normal levels of serum gastrin.

J. L., a 46-year-old man, complained of fatigue and sexual impotence for one year. Physical examination was normal except for hypertension (160/105). Serum calcium values ranged between 11.6 and 12.5 mg% and serum phosphorus values ranged between 1.3 and 2.3 mg%. Plasma parathormone levels were repeatedly elevated with higher levels in the left jugular venous samples than in the right (left 460 ng/ml; right 280 ng/ml). TRP ratios were 52, 36, and 50%. There was gastric acid hypersecretion (13 mEq/hr basally and 26 mEq/hr after histalog stimulation); the G-cell population of the antral mucosa was markedly increased (10 to 12 G-cells/acinus). Basal serum gastrin values (56 to 85 pg/ml) were not significantly altered in response to feeding or administration of glucose, arginine or insulin. Other studies revealed mild glucose intolerance, a Type IV hyperlipoproteinemia, and normal thyroid and adrenocortical parameters. Radiologic examinations of the chest, sella, hands, kidneys, gallbladder were normal; upper gastrointestinal radiologic examination demonstrated a thickened wall in the second portion of the duodenum without ulceration.

A left parathyroid adenoma and a right normal parathyroid gland were surgically removed, following which serum calcium and phosphorus levels and TRP ratios returned to within normal ranges. The plasma parathromone determinations indicated undetectable values immediately postoperatively and have remained so. Three years following parathyroidectomy gastric acid

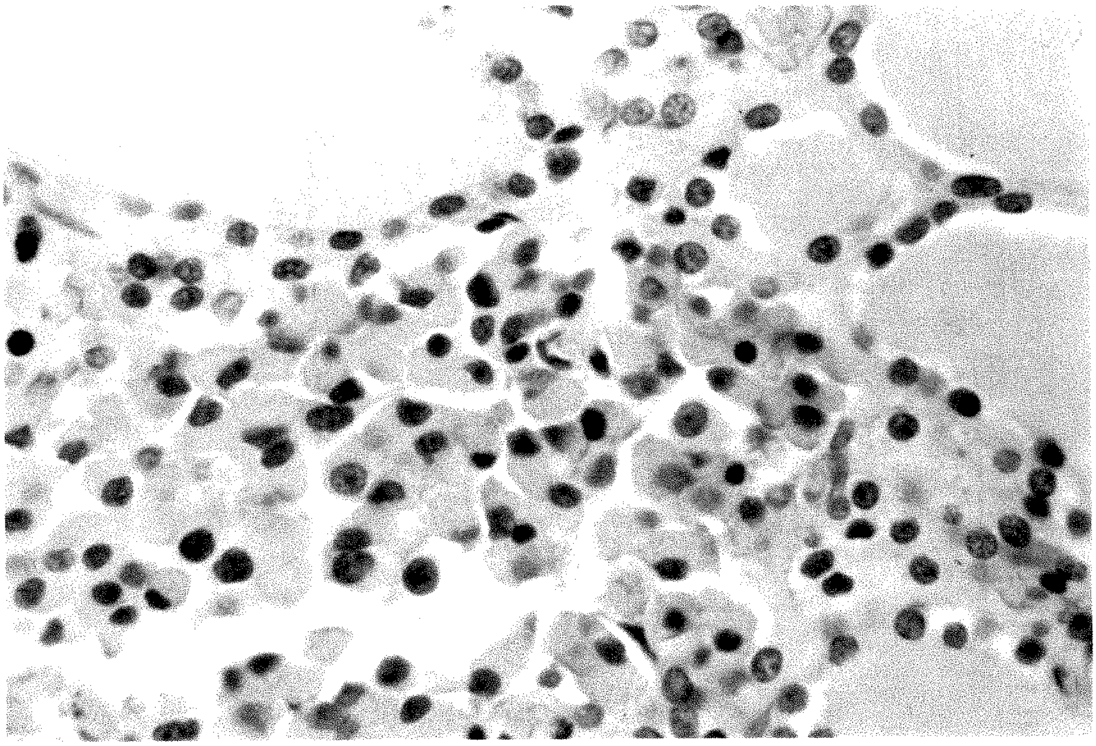

FIG. 11. Photomicrograph illustrating the hyperplasia of calcitonin-secreting, parafollicular (C) cell tissue of the thyroid gland found at the time of autopsy in patient L. R.

secretion has returned to normal values and the serum gastrin values ranged from 43 to 83 pg/ml and were not responsive to intravenous secretin. Antral G-cell hyperplasia persists in this patient after parathyroidectomy and correction of hypercalcemia.

Comment: Antral gastrin cell hyperplasia may be the reason for the relatively high incidence (15 to 20%) of acid-peptic duodenal ulceration and acid hypersecretion in primary hyperparathyroidism although, to date, this finding has been implicated only by association.[4,36] The consistently low normal serum gastrin levels are comparable to those observed in patients with duodenal ulcer. The persistence of the antral G-cell hyperplasia after the reversal of the hypercalcemia and gastric hyperacidity suggests that the hyperplasia may be developmental, rather than adaptive to its environment. Certainly many more patients such as have been reported[6] with various types of hyperparathyroidism need to be studied prospectively, before and after parathyroidectomy, to clarify the association of antral and parathyroid abnormalities. An exceptional instance of a gastrin-containing parathyroid adenoma with hypergastrinemia causing the Zollinger-Ellison syndrome has been described.[45]

Case 8. Diagnosis: Familial multiple endocrine adenomatosis syndrome, adenomatous Cushing's syndrome, malignant Zollinger-Ellison syndrome; temporary tumor regressions after total gastrectomy and hypophysectomy; clinically unsuspected associations of APUD cell hyperplasias of the pancreatic islets, parathyroid glands, thyroid parafollicular cells, and the opposite adrenocortical gland. This patient has been reported in part previously,[12] but is included here to add the findings of the developed hyperplasias before his death, 19 years after his first endocrine symptoms.

Patient L. R., (Fig. 10), a 36-year-old male, presented first with duodenal ulceration and Cushing's syndrome, for which a right adrenocortical adenoma was excised (1955). A metastatic, non-Beta islet cell carcinoma with Zollinger-Ellison syndrome required total gastrectomy (1961). This was followed by apparent regression of metastatic tumor, as observed by an abdominal second-look procedure and low bio-assay values of serum gastrin. Six years later cervical and mediastinal metastases were excised. Seven years after total gastrectomy, at a time when all of the biopsied mediastinal tumor could not be completely removed, a surgical hypophysectomy (histologically normal) was done (1968). There was a second period of visible tumor regression over a 5-year period, associated with a fall in immunoassayable gastrin from approximately 1500 pg/ml to 700 pg/ml in the first 2 years. In 1969 an excision of a cervical mass revealed parathyroid hyperplasia; there had been no clinical evidence of hyperparathyroidism nor hypercalcemia. There were no further problems until in 1973, within a month of his death, (18 years after his first endocrine operation), he showed signs of acute hypopituitarism, hypoglycemia, weakness, and sudden massive mediastinal spread of metastases which did not respond clinically to streptozotocin or x-radiation. A fall in the immunoassayable serum gastrin from 3676 to 450 pg/ml occurred while on streptozotocin therapy, at which level the serum gastrin remained until his death. Post-mortem examination revealed islet cell hyperplasia (nesidioblastosis), metastatic islet cell carcinoma to the periaortic mediastinal and cervical lymph nodes, (none remained in the liver), chief cell hyperplasia of two remaining parathyroid glands, parafollicular (C) cell hyperplasia of the thyroid gland (Fig. 11), subtotal absence of the pituitary gland, and nodular hyperplasia of the remaining adrenocortical tissue. The mediastinal tumor contained no gastrin on immunochemical assay. Familial involvements in this patient have been reported previously.[13]

Comment: This complicated clinical course illustrates the protracted and metachronous involvement of the foregut endocrine abnormalities ranging from hyperplastic to neoplastic changes over at least a 19-year period. Regressions of tumor and clinical remissions seemed to be associated with treatment, including total gastrectomy and hypophysectomy, while recurrences appeared to be associated with subsequent development of further pluroglandular hyperplasias. After total gastrectomy, at which time a liver metastasis had been excised for biopsy, liver involvement was never again seen, a phenomenon still unexplained. For the most part of the 19 years of studies and operations, the patient led a useful and happy life as a postman in his community.

Discussion

The clinical and laboratory observations in these patients were made in a prospective fashion for the most part, except where retrospective review of tissues was indicated. The purpose of reporting the findings as they are observed is to document them, even though the precise interpretation of the observations may not be possible or even correct. Surely further observations by clinicians and investigators will require re-evaluations and assessments with the passage of time. The information gained to date seems to suggest that embryologic errors in development can explain many of the bizarre features of foregut endocrinopathies; modifications of known syndromes are possibly related to associated endocrine cell hyperplasias which may attend alterations in environmental homeostasis. Treatment of the Zollinger-Ellison syndrome, especially by total gastrectomy, may reverse imbalances in feedback systems so that remissions of the syndrome, and even tumor regressions, are occasionally observed. Hypophysectomy, employed on only one occasion, resulted in only a temporary 5-year remission and regression, before a sudden and fulminating growth of a non-gastrin-containing mediastinal tumor occurred in this familial, genetic type of multiple endocrine adenomatosis syndrome in Case 8. Whether the ulcerogenic tumor is located entopically or ectopically in the Zollinger-Ellison syndrome, the treatment by total gastrectomy continues to yield beneficial results in terms of control of the ulcerogenic potential, of tumor suppression, and of ultimate survival for most patients.[9]

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DISCUSSION

DR. ROBERT C. HICKEY (Houston): Dr. Friesen and Dr. McGuigan have put together a very thoughtful presentation. These authors have described eight patients with varying endocrine excesses, some overtly polyglandular, and having in common foregut APUD cell proliferation.

In the disorders of the polyendocrine excess it's difficult at times to put it all together. There are probably three main groupings. Dr. Wells has referred to one, MEA II, and Dr. Zollinger is very familiar with the MEA I; and further, there's ectopic hormone production, usually of incomplete hormones, by malignant non-endocrine tissues and even at times by endocrine tissues.

Orderly thought can become very confusing. When a tumor of neuroectodermal origin as the parafollicular thyroid cells of Nonidez (1932) or the APUD cells of Pearse (as has been discussed here) produces also another peptide, as a hormone-like ACTH substance, the result is a florid corticoid excess over-production of a steroid. Dr. Friesen might comment upon his patient that potentially had this type of disorder.

In this polypeptide hormonal disease array, I wish to present another syndrome, published recently from the Anderson that should probably be grouped with the MEA I: a syndrome of an identified carcinoid tumor of the foregut, with a parathyroid adenoma, and circulating calcitonin excess.

The calcitonin was not coming from the thyroid neuroectodermoid C-cells. This fact was proved, I believe, by transfemoral venous catheterization very much from a technical viewpoint as has been described to you by Dr. Wells. The neck venous effluent showed a parathyroid hormonal differential but not a calcitonin differential. We reasoned that the other tumor, the carcinoid, was producing the calcitonin. There is precedent for this, as you know, in carcinoid tumors elsewhere. It may well be that we are dealing with a systemic disease.

DR. WALTER BALLINGER (St. Louis): I certainly enjoyed this paper and presentation of an extremely complex subject with the multiple presentations of these fascinating apudomas.

We certainly must agree however that many of them are accompanied by severe hyperchlorhydria, that many of them present with metastases and nodal metastases and at least one case presented today, this patient was elderly and you were reluctant to perform a total gastrectomy.

We were not informed however as to how these patients died. Whether they did of their metastases or their ulcer diastheses.

Many patients, as we've known for years, die of the ulcer diasthesis, in absolute misery, with bleeding and perforation, unless a total gastrectomy can be performed.

I rise to mention only, that in this situation, a new drug is available, metyamide, with which many of us are familiar. It's an H-2 antagonist, a blocking agent which prevents massive outpouring of gastric acid and allows some of these patients to survive somewhat longer without the complications of their ulcer diathesis and I would ask whether this has been used in the present series as a palliation, with that of streptozotycin.

DR. ROBERT M. ZOLLINGER (Columbus, Ohio): I think as we see an increasing number of immunoassays develop, it will help us to resolve some of the difficulties we've had in making the diagnosis in these patients.

In general, I think when we have an elevated fasting gastrin, and certainly after calcium infusion when the gastrin level is tripled, we'd be inclined to think that that patient has a gastrinoma or islet cell tumor some place, even though we can't find it at the time of surgery.

Secondly, Dr. Friesen, I continue to remain a little bit anxious about the diagnosis of antral-G-cell hyperplasia. I don't know whether these cells you talk about are migrating to the antrum causing this or not, so I'd feel better if you'd tell me about that.

Now, it's true of course that some of these cases have multiple polypeptide producing-tumors, and I think we're going to find out more and more about these cases as a result of his studies.

We hope he will continue to have his concern for these cells and their nomadic habits so that eventually we can more easily understand these mysterious polypeptide-secreting cells. I'd like to ask how frequent he feels there's an extra-pancreatic source for the production of gastrin.

DR. STANLEY R. FRIESEN (Closing discussion): Dr. Hickey brings up the various multiple endocrine adenomatosis (MEA) syndromes and points out again that there can be cross-overs in the MEA I and the MEA II. As a matter of fact, he has written a very nice paper on the calcitonin-secreting carcinoid tumors of the foregut. The cross-overs are usually in the area of the parathyroid gland and the parafollicular cells of the thyroid gland.

There also seems to be another cross-over area in the adrenal cortex. Cortical hyperplasias and adenomas, relative to the first paper this afternoon, have been reported in both MEA I and in MEA II. I think they're probably related to ACTH stimulation from another source, pituitary or ectopic.

Dr. Ballinger raises an important question about how these patients die. Only two of these patients I'm describing today are dead. The eight-year-old boy with ectopic parathormone elaboration died of massive tumor ascites and respiratory involvement. We were going to give him streptozotocin, but he developed nephropathy and we were not able to treat him with streptozotocin, which in the literature has been reported to be effective in islet cell tumors secreting parathormone.

None of these patients died of the Zollinger-Ellison syndrome. The last patient in this report, a 19-year survivor, did not die of the Z-E syndrome. He had had a total gastrectomy, but later he did have recurrent tumor, but it did not contain gastrin; he died with polyendocrine hyperplasias which developed just prior to his death.

Many of these patients, if they live long enough, are going to develop hyperplasias of whatever endocrine cells they have left, in my opinion.

Total gastrectomy for the Zollinger-Ellison syndrome remains the best form of treatment, not only for the acid diathesis but for the tumor, and for the actual survival of patients.

We have not had occasion to use metiamide, the H-2 receptor inhibitor, which I think will surely be the treatment some day for severe Zollinger-Ellison syndrome. As you know, its use is controlled and it can be used only in those situations in which a total gastrectomy cannot be done.

Dr. Zollinger, thank you again for your provocative comments which should tempt me to digress momentarily from the foregut to the hindgut. As all of you know, Dr. Zollinger stimulated many questions when he first suggested another source for gastrin other than the antrum, before this Association 20 years ago; he is still provoking important questions and we are trying to get some of the answers as to the mechanisms of development of these unusual syndromes.

I'm confident about the migration of cells. I'm not confident about why these cells become hyperplastic. Is it genetic, or do they become hyperplastic in compensation, or as an adaptation to an environment that they're in?

For instance, if a patient has chronic duodenal ulcer with chronic hyperacidity of acid, and acid is bathing his duodenum for a period of ten or 15 years, what's going to happen to that patient's secretin response during this chronic stimulation of the duodenum, or the chronic inhibition of the antrum?

The measurement that we use for G-cell hyperplasia is a rough quantitation, but it can be measured more accurately by means of immunofluorescence with or without television scanning. It's much simpler, however, to get a toluidine blue stain on glutaraldehyde-fixed biopsies in order to identify G-cell hyperplasia in the middle layer of the antral mucosa.

Glycerol:

Major Contributor to the Short Term Protein Sparing Effect of Fat Emulsions in Normal Man

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Intravenous fat emulsions have been advocated as acceptable alternatives to hyperosmolar glucose solutions in parenteral nutrition. The ability of a fat emulsion (soy bean oil suspended in glycerol) to produce nitrogen sparing in the absence of nitrogen intake was examined in normal man. The protein conservation obtained by the fat emulsion can be duplicated by the infusion of glycerol alone in the same amount as that available from the fat emulsion.

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INTRAVENOUS FAT EMULSIONS have been advocated as an effective form of intravenous nutritive support for the past 25 years.[8,11,12,16,17,27,28,38] All of these studies have combined cotton seed or soy bean emulsions as the fat source with other energy substrates (usually glucose), as well as amino acids.

Earlier studies in the United States with cotton seed oil emulsions were largely discontinued because of the adverse side effects.[1,35] As the fat emulsion from soy bean* became available, it was re-examined, prior to being released for general use.

In our preliminary studies with this emulsion as a solitary substrate,[2] difficulty in interpretation resulted because of the inability to distinguish the effects of the fat emulsion from the effects of the contained and available glycerol. An infusion of 3 gm/kg/day of Intralipid® in a 67 kg man could provide as much as 71 gm of glycerol, 50 gm added as free glycerol and 21 gm in ester form in the triglyceride. The following study examines the protein-sparing ability of Intralipid® infusion as against glycerol infusion alone in normal man.

Material and Methods

Six normal, healthy male volunteers (ages 21-36, weight Group I=71.5 ± 6.5 kg, Group II=73.1 ± 6.1 kg, mean BSA=1.98 ± 0.09 m^2), were interviewed, examined and submitted to biochemical screening to ensure normality. Procedures and risks were carefully explained to each subject and signed informed consent obtained. The volunteers were then divided into two groups of three each: the three groups underwent the identical experimental protocol. In both groups, a 4-day stabilization period on standard diet was carried out prior to the study (3 days as outpatients, 1 day as in-patients). Group I received fat emulsion (1gm/kg/day) for the first 4 days over 8 hours, and then in higher dose (3 gm/kg/day) for the second 4 days over 20 hours. Group II received only glycerol in saline, in amounts calculated to provide the quantity of glycerol that was available from the exogenous glycerol contained in Intralipid®, plus that available

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*Soy bean emulsion. Intralipid® Vittrum Coy, Stockholm, kindly made available by Cutter Laboratories, Berkeley, California.

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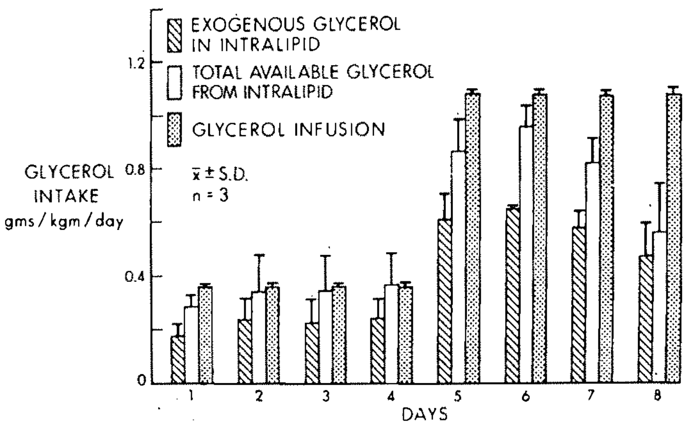

FIG. 1. Glycerol intake. Both the intralipid infusion and the glycerol infusion groups received comparable intakes of glycerol at two dose levels.

from total hydrolysis of the administered triglyceride (Fig. 1). Glycerol was infused over 24 hours.

Intralipid® ingredients are shown in Table 1. Both groups received nothing by mouth except distilled water for the duration of the study.

Analyses

Urine was collected each 24 hours and analyzed for urea nitrogen, creatinine, uric acid (all Auto Analyzer),* total nitrogen (Kjeldahl), sodium, potassium (emission spectrophotometry), calcium, and magnesium (atomic absorption spectrophotometry). Venous blood samples were obtained at 8 a.m. and 2 p.m. on alternate, successive days. Serum sodium, potassium, calcium, magnesium, triglycerides, glycerol, free fatty acids, (Dole extraction method), blood urea nitrogen, glucose (Auto-Analyzer, ferricyanide reduction), serum immune reactive insulin, glucagon (double antibody technique), blood ketones, lactate, pyruvate, and alanine (enzymatic) were determined. The free glycerol and triglyceride method was by enzymatic determination of NADH consumption.† Serum samples were cleared of the turbidity present in the latter days of the lipid infusion, by proceeding as for saponification but without addition of heat. The sample was then immediately centrifuged and the free determination performed as in the standard method. Respiratory quotients were determined by analysis of expired gas twice each hour during 10-16 hours of the awake day as in previous studies from this laboratory.[3]

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*Technicon, Inc., Tarrytown, NY.
†Boehringer Corp.

TABLE 1. *Intralipid Ingredients*

Soybean Oil	100 gm/L
Phospholipids	12 gm/L
Glycerol (Free)	25 gm/L
pH	7-8.5
Osmolality	280-300 mosm/kg/H_2O

TABLE 2. *Caloric Intake: Calories/Day**

Day	Lipid Infusion	Glycerol Infusion
1	626 ± 80	115 ± 12
2	794 ± 248	115 ± 12
3	777 ± 263	115 ± 12
4	855 ± 229	115 ± 12
5	2038 ± 390	346 ± 37
6	2233 ± 127	346 ± 37
7	1940 ± 294	346 ± 37
8	1595 ± 502	346 ± 37

*(mean & s.d.)
n=3

Calculations

The calculated available calories for each regimen are depicted in Table 2. Calculation of calories derived from Intralipid® is based on 9.0 Cal/gm for the contained fat, and 4.1 Cal/gm for the exogenous hydrated glycerol. In the glycerol infusion only, caloric equivalence is calculated at 4.3 Cal/gm. Glycerol available from total hydrolysis of the administered fat emulsion was calculated as 21 gm of glycerol from each 200 gm of administered emulsion. The nitrogen contained in Intralipid® (a mean of 0.16 gm/day) is not included in the nitrogen balance. Phosphorus intake was calculated on the basis that the lipid solution contained 0.45 mg/ml of phosphorus.

Total glycerol in Group I was comparable to the exogenous glycerol infusion (Group II). On the last day of the study the glycerol infusion group received more glycerol than was available from the lipid infusion (52 ± 19 v. 80 ± 9 gm) (Fig. 1). The total calories in each infusion differed five-fold (Table 2).

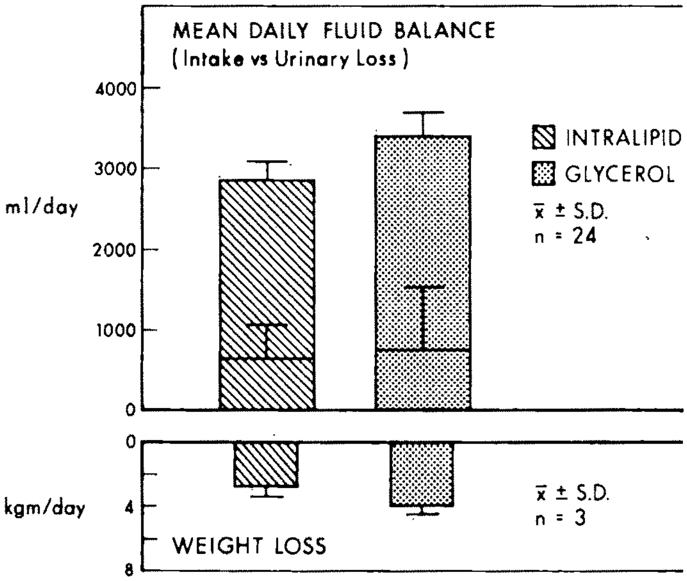

FIG. 2. Intralipid and glycerol infusion in normal man: Fluid Balance and Weight loss. Comparable balance was seen in both regimens. Weight loss was greater in the glycerol group.

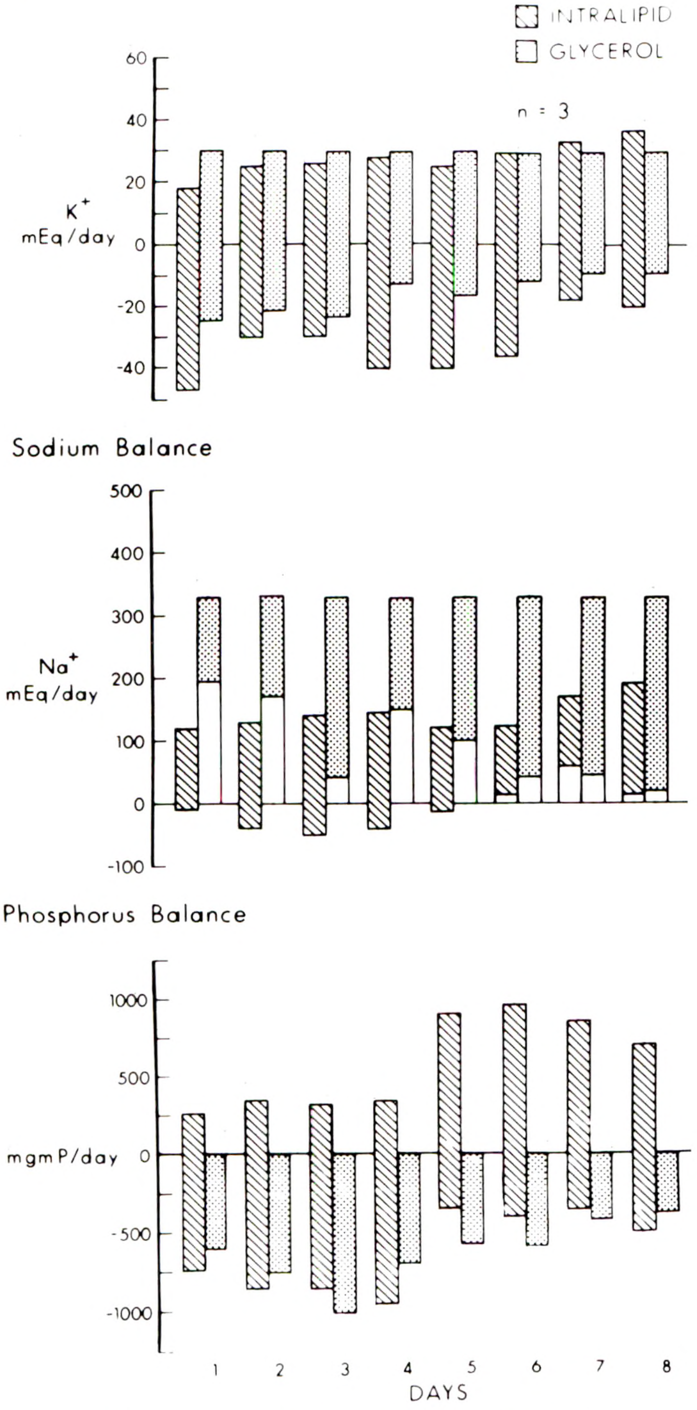

FIG. 3. Sodium, potassium and phosphorus balance.

Results

There were no untoward reactions or side effects to any of the infusions in any volunteer. Hematocrit, hemoglobin and liver function tests at the end of 8 days of infusion were not different from controls in any subject. Hemoglobin was not determined on the turbid samples.

All results are mean ± s.d., n=3, and statistical comparison by Student's 't' test unless otherwise stated.

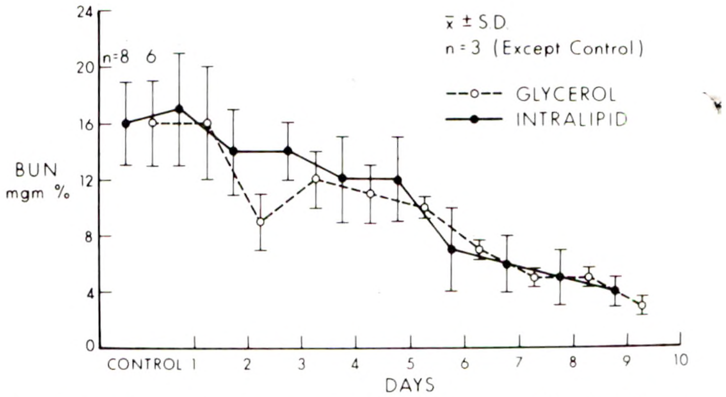

FIG. 4. Blood urea nitrogen response. Identical progressive diminution is noted, and confirmed by covariance analysis.

Mean total weight loss was 2.86 ± 0.8 kg (Group I) and 4.1 ± 0.5 kg (Group II) (Fig. 2).

Sodium balance (Fig. 3) was negative for the first 4 days of the lipid infusion, but positive on all other days for both groups. There was considerable variation in sodium intake, as attempts to keep volume intake constant using only saline were made (Fig. 2). Potassium balance (Fig. 3) remained consistently negative in both groups, and there was not statistical significance between the two small groups. Calcium and magnesium levels fell progressively, while serum phosphorus was unchanged (Table 3). Phosphorus balance remained negative in both groups (Fig. 3). Blood urea nitrogen fell in both studies

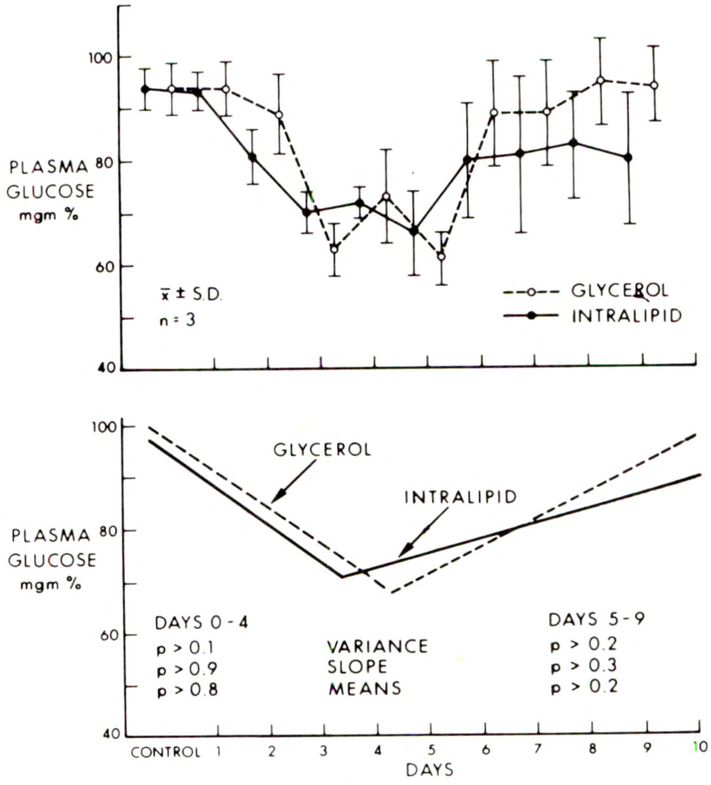

FIG. 5. Plasma glucose response, and covariance analysis.

TABLE 3. *Intralipid® and Glycerol Infusions in Normal Man*

	P		Mg		Ca	
Day	Lipid	Glycerol	Lipid	Glycerol	Lipid	Glycerol
0	3.3 ± 0.3	3.2 ± 0.3	1.9 ± 0.2	2.0 ± 0.2	9.6 ± 0.3	10.6 ± 0.2
1	2.8 ± 0.2	2.7 ± 0.6	1.9 ± 0.1	2.1 ± 0.1	9.5 ± 0.4	9.9 ± 0.4
2	3.0 ± 0.4	2.5 ± 0.4	1.8 ± 0.1	1.9 ± 0.1	9.3 ± 0.2	9.7 ± 0.3
3	3.1 ± 0.2	2.7 ± 0.5	1.8 ± 0.1	1.8 ± 0.0	9.3 ± 0.5	9.8 ± 0.2
4	3.1 ± 0.3	2.7 ± 0.5	1.7 ± 0.1	1.7 ± 0.1	9.1 ± 0.4	9.7 ± 0.3
5	3.0 ± 0.1	2.7 ± 0.4	1.7 ± 0.2	1.7 ± 0.1	9.2 ± 0.4	9.8 ± 0.3
6	2.8 ± 0.3	2.6 ± 0.4	1.6 ± 0.2	1.5 ± 0.2	9.1 ± 0.2	9.4 ± 0.3
7	3.1 ± 0.3	2.8 ± 0.3	1.6 ± 0.2	1.4 ± 0.2	9.0 ± 0.4	9.1 ± 0.2
8	2.8 ± 0.2	2.9 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	8.8 ± 0.7	9.7 ± 0.3
9	3.0 ± 0.1	2.8 ± 0.2	1.6 ± 0.2	1.4 ± 0.3	8.8 ± 0.3	9.6 ± 0.2

Note: P=Serum Phosphorus; Mg=Magnesium; Ca=calcium; (mean ±s.d., n=3)

(Fig. 4) consistent with a protein free diet. Covariance analysis shows that the mean, slope and form of the decline in blood urea is identical in both groups. Blood glucose showed an initial fall during low dose infusion, followed by a rise during high dose infusion. Covariance analysis in both groups shows an identical pattern (Fig. 5).

The triglyceride (TG) levels were elevated throughout the fat emulsion infusion but were unchanged from control values during the glycerol infusion (Table 4). Free fatty acid (FFA) levels were elevated throughout the lipid study and were elevated initially in the glycerol study and then fell to levels which were probably consistent with the degree of fat mobilization taking place for endogenous energy supply. Glycerol (GLY) levels were higher, as expected, in the glycerol infusion and reflected rates of utilization; accumulation in plasma was not noted, suggesting that the ability to metabolize glycerol was not exceeded. The changes consequent upon the 8 a.m. and 2 p.m. sampling, the latter coinciding with a period of substrate infusion, is clearly seen in both FFA and GLY blood levels (Table 4).

Insulin levels in the glycerol study fell minimally but progressively from 16 ± 2 (day 1) to 13 ± 1.0 μU/ml (day 9) (P=0.08). In the lipid group 2 of the 3 subjects displayed unchanged insulin levels (13 ± 6 to 16 ± 3 μU/ml) throughout the study. The third subject had markedly elevated levels on the last 3 days of the study (147-222 μU/ml), which were not able to be repeated in an alternative assay. Glucagon levels were unaltered by the glycerol infusion. Peripheral venous alanine levels followed glucose change with significant ($P<0.05$) diminution from control on days 3, 4 and 5 (Fig. 6). Venous alanine levels were not obtained in the lipid study.

Betahydroxy-butyrate levels were rapidly elevated by lipid infusion reaching a maximum of 2.84 ± 0.34 mM/L on the 9th day. A milder elevation was seen in the glycerol infusion to 0.456 ± 0.094 mM/L. Acetoacetate followed a similar pattern being maximally elevated on day 9 to 0.465 ± 0.02 mM/L in the lipid infusion but only to 0.068 ± 0.006 mM/L in the glycerol group.

Venous lactate levels were unchanged in the lipid group; day 1, 452 ± 135 μM/L day 8, 398 ± 45 μM/L. During glycerol infusion lactate rose to 966 ± 78 μM/L by the eighth day ($P \pm 0.001$, when compared to day 8 of the lipid infusion). Pyruvate levels fell in the lipid study; (37 ± 10 μM/L on day 1 to 22 ± 7 μM/L on day 8), and remained unchanged in the glycerol study 44 ± 2 (day 1) to 44 ± 14 μM/L (day 8) ($P<0.001$ for lipid vs. glycerol on day 8). respiratory quotients fell progressively to 0.65-0.70 in both studies.

The most striking results are seen in the urinary nitro-

TABLE 4. *Intralipid and Glycerol Infusions in Normal Man: Triglyceride, Free Fatty Acid and Glycerol Levels (mean ± s.d. n=3)*

		TG mg%		FFA mEq/L		GLY mg%	
Day	Time	Lipid	Glycerol	Lipid	Glycerol	Lipid	Glycerol
0	8am	88 ± 46	94 ± 35	707 ± 121	676 ± 175	1.3 ± 1.0	1.2 ± 0.2
1	8am	57 ± 51	95 ± 19	676 ± 326	633 ± 78	1.3 ± 0.6	1.0 ± 0.2
2	2pm	294 ± 236	83 ± 16	2261 ± 275	865 ± 263	3.2 ± 1.2	5.1 ± 1.7
3	8am	105 ± 50	110 ± 20	1915 ± 684	1680 ± 510	1.1 ± 0.4	1.6 ± 0.5
4	2pm	362 ± 189	118 ± 4	2036 ± 69	1345 ± 493	3.0 ± 0.5	4.4 ± 2.0
5	8am	128 ± 42	156 ± 17	1802 ± 435	1630 ± 83	1.7 ± 0.5	1.6 ± 0.9
6	2pm	713 ± 410	102 ± 7	1921 ± 509	1380 ± 262	6.3 ± 0.6	3.8 ± 0.6
7	8am	588 ± 212	116 ± 8	1697 ± 420	838 ± 242	1.2 ± 0.5	4.0 ± 1.0
8	2pm	685 ± 223	90 ± 15	2130 ± 1532	963 ± 319	2.8 ± 0.8	4.5 ± 1.7
9	8am	537 ± 89	104 ± 11	1980 ± 540	720 ± 226	1.9 ± 1.1	4.0 ± 1.7

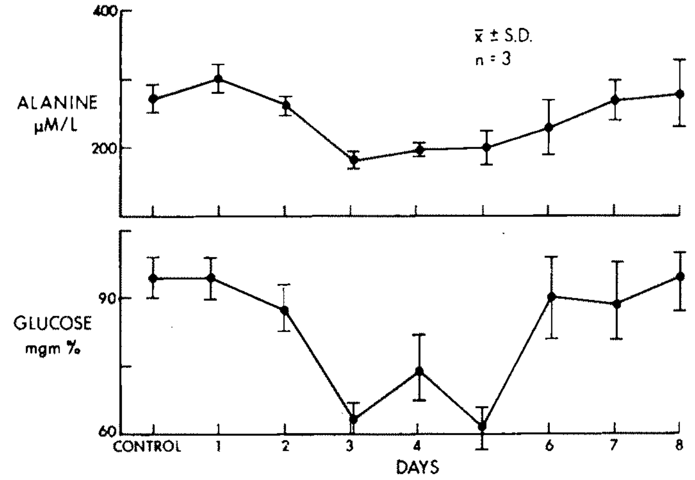

FIG. 6. Alanine and plasma glucose response.

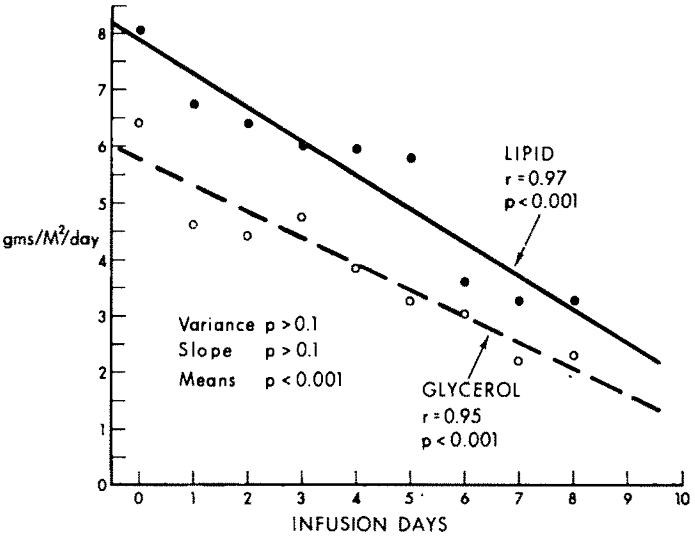

FIG. 8. Urinary total nitrogen, covariance analysis. ($\bar{x}$, n=3).

gen data. The urinary total nitrogen (UTN) values fell progressively in both studies from a mean of 6.73 to 3.26 gm/m^2/day for Group I and 6.38 to 2.28 gm/m^2/day for Group II (Fig. 7). Covariance analysis shows there to be no difference between the two groups although the mean for the glycerol group is significantly lower ($P<0.05$) (Fig. 8). Urinary urea nitrogen (UUN) progressively diminished in both groups of comparable magnitudes (Fig. 9). Urinary creatinine excretion was unchanged throughout.

During glycerol infusion urinary uric acid fell from 511 ± 165 mg/day on day 1 to 221 ± 87 mg/day on day 4 ($P=0.05$), and then rose to 536 ±147 mg/day on day 8 ($P=0.03$ cf. to day 4) consistent with glycerol's known uricosuric effect.[13]

Comparative changes in UTN in response to different protein free regimens is shown in Fig. 10. The glucose infusion data has been previously reported from this laboratory[24] and the starvation data are that of Cahill and co-workers done in conjunction with this laboratory.[3] The efficacy of glycerol as a nitrogen sparer at low caloric equivalence is apparent.

Discussion

The present study suggests that the nitrogen sparing seen when intravenous fat emulsion (Intralipid®) is given as a sole substrate can be reproduced totally by the infusion of an equivalent amount of glycerol alone. In the absolute end analysis the experiment would need to be repeated with triglyceride without other contained substrate. The return of glucose levels to near normal in the latter part of the present study is consistent with glycerol's role as a gluconeogenic source, but decrease in

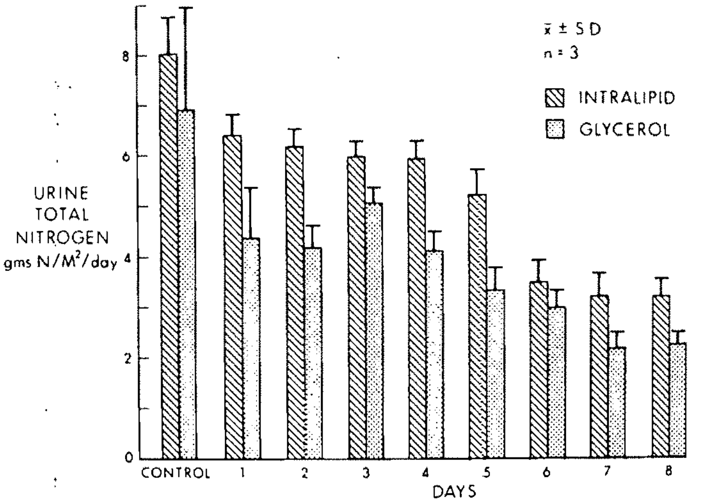

FIG. 7. Urinary total nitrogen response.

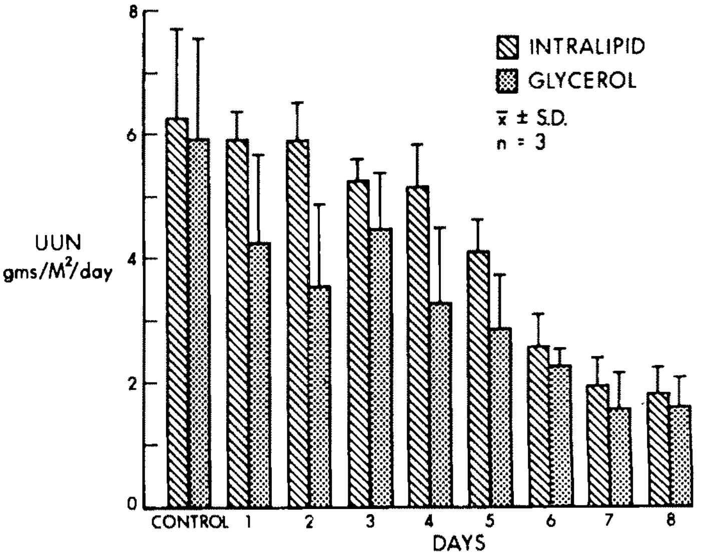

FIG. 9. Urinary urea nitrogen response.

peripheral utilization cannot be excluded. Other authors have both noted plasma glucose rise with high glycerol loads[31] intravenously and noted no change in glucose although the infused glycerol forms a greater percentage of total hepatic glucose precursors.[37]

Using glycerol uniformly labeled with Carbon-14 and determining incorporation of C^{14} into plasma glycerol and glucose, it has been shown that glycerol is inhibitory to the conversion of other gluconeogenic substrates such as lactate, pyruvate, and amino acids to glucose.[32]

In the present study lactate levels were elevated during glycerol infusion, a situation not seen with intravenous glycerol as an acute infusion.[30] Oral glycerol when given to fasting healthy subjects at 1 gram per kilogram per day did not result in elevation of blood glucose; free fatty acids were slightly increased as was the immune reactive insulin.[39] This insulin rise was thought to be due to gastrointestinal hormonal stimulation of insulin release. In a similar manner oral glycerol given as 25 to 50 grams 4 times a day can result in decrease in ketone bodies and appears to be a carbohydrate not requiring insulin for that effect.[9]

It has previously been shown in animals that acute elevation of free fatty acids using fat emulsions with heparin results in a decrease in hepatic glucose production. This decrease in hepatic glucose production is accompanied by a 30% inhibition of peripheral glucose utilization.[31] Associated with the free fatty acid elevation in the studies of Seyffert[31] there was an increase in insulin production and a decrease in glucagon production, events not seen in the present study, except for the insulin level elevation in a single subject on the last two days of his lipid infusion. In this particular subject there was not a commensurate elevation of free fatty acid level. In the previously mentioned study[31] an increase of free fatty acid levels from 536 to 1830 mEq/L was associated with a fall in arterial glucose of 14 mg%. A FFA rise of less than 300 mEq/L was not associated with changes in insulin or glucagon. This, however, cannot be the explanation for the absence of insulin and glucagon changes in the present study, as on all occasions the elevation of free fatty acid levels was considerably greater than 300 mEq/L.

The physiology of oral glycerol has been reviewed[13] as has the ability of the liver to handle glycerol.[29] Many of the studies have examined the side effects of high doses of glycerol,[10,34] and glycerol has been used many ways to decrease cerebral edema.[4,18–20] All side effects appear to be associated with high dosage, rapid rate infusions without added electrolytes.

The more fascinating findings of the present studies refer to the changes in protein metabolism. These observations bring to focus the many classical studies which have examined the effect of fat on nitrogen sparing. In 1909, Cathcart studied a colleague, Dr. T. Graham Brown, substituting fat for carbohydrate as total dietary intake.[5] After 4 days of 2736 calories as carbohydrate, the volunteer received 3645 calories as fat. Urine nitrogen rose from 4.34 to 4.83 and then 8.3 grams per day on successive days. Urea nitrogen similarly rose from 3.31 to 3.76 to 6.64 grams per day. Examining the effect of substituting fat for carbohydrate, in rats on fixed protein intakes, Thompson and Munro[33] noted a deterioration in nitrogen balance when carbohydrate was wholly or partially replaced. The increased nitrogen output was transitory and returned to its former level after a period of adaptation. This confirms the concept put forward by Cathcart[6] that "isotamieutic" or "isoeconomic" is not equivalent to "isodynamic," i.e. equality of nitrogen sparing (or "husbanding") is more physiological than equality of energy availability.[6] In studies done on themselves, Cuthbertson and Munro showed that there was increased nitrogen sparing by superimposing extra calories as carbohydrate on a base of a 15 gram nitrogen diet, that was not seen when the same addition of excess calories was given in the form of fat.[7] In extensive reviews of the subject[21,23] the many problems of experimental design, species variability, duration of regimen and synchronicity of substrate have all been examined. Evidence suggests that under conditions of caloric deprivation, but adequate protein intake, nitrogen balance is influenced by changes in energy intake, whether they come from alterations in dietary carbohydrate or in dietary fat,[22] although milligrams of nitrogen spared per calorie of carbohydrate is generally better than millirams of nitrogen spared per calorie of fat.

In short term studies, substitution of fat for carbohydrate results in a deterioration in nitrogen balance; in the long term, nitrogen sparing by fat alone may become manifest. It has been shown that in protein deficient

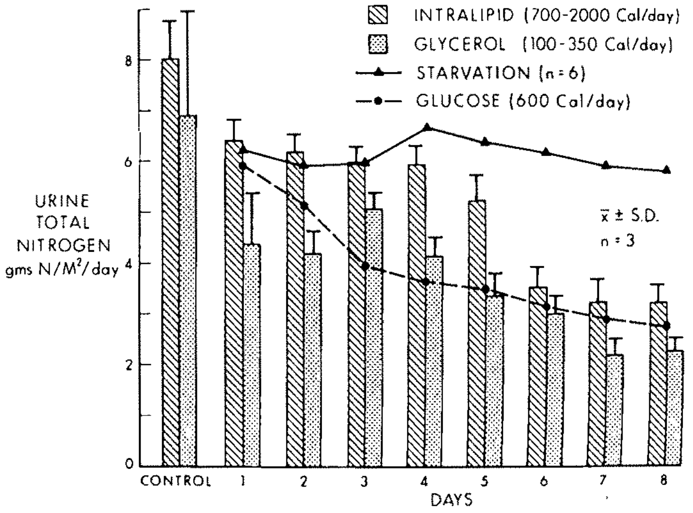

FIG. 10. Comparative urinary nitrogen excretion under different regimens, with different caloric intakes and different substrates.

diets, substitution of fat for carbohydrate results in an increase in urinary nitrogen output which lasts for about 10 days but is then not further prolonged.[21] Such results may be interpreted that in protein free diets, fat has a great deal less nitrogen sparing action than the same amount of carbohydrate. This is consistent with the lesser insulin response evoked and that it requires time for the initally obligatory glucose users to adapt to the use of ketone bodies.[26]

In animal studies it has been clearly shown that nitrogen balance on Intralipid® as a sole substrate is worse than that obtained by amino acids alone at half the calories.[14] When fat emulsions were infused into two volunteers on a marginal protein intake,[35] nitrogen balance was improved by the addition of 930 calories as intravenous fat. The emulsion did contain a small amount of carbohydrate. In the same study when the nitrogen intake was lowered to 3 grams per day no improvement in nitrogen balance could be shown by the addition of even 1200 intravenous calories as fat. Other investigators who used a cotton seed oil emulsion, on a protein free diet in 6 patients, showed that fat (1800 and 2700 calories per day) was better than intravenous dextrose (200 calories) in diminishing urinary nitrogen. The majority of other studies involved soy bean emulsion given in conjunction with other substrates besides protein.[8,16,25–27,36,38] The substrates were usually glucose. Nitrogen balance data are not given in many of these studies but positive nitrogen balance has been obtained in some.[27,28,38] Using fat and carbohydrate in varying proportions, others have shown that nitrogen sparing was proportional to the glucose intake with no effect related to the amount of infused fat.[15]

The present study has re-emphasized the experimental difficulties in determining the relative contribution of fat and carbohydrate to protein sparing in man. The study has emphasized that in the short term the commercially available preparation Intralipid® given at two dose levels diminishes urinary nitrogen excretion. The contribution of the fat to this decrease in urinary nitrogen appears to be minimal, the same diminution of nitrogen excretion can be obtained by infusion of glycerol alone in quantities similar to the amounts contained within Intralipid®.

It appears that in the absence of an adequate protein intake, the degree of nitrogen sparing provided by high calorie triglyceride infusion, can be simulated by low calorie carbohydrate infusion. The special role of glycerol as an energy source when combined with synthetic amino acids as a peripheral nitrogen source remains to be examined.

Acknowledgements

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DISCUSSION

DR. STANLEY M. LEVENSON (Bronx, New York): At first hearing, the findings regarding protein metabolism as reflected by blood urea levels and urinary nitrogen excretions seem unexpected; namely, the provision of at least five times less potential exogenous calories as glycerol has the same or even possibly greater protein sparing effect than the intravenous fat emulsion, and that the protein sparing effect of the latter can be interpreted as due entirely to its glycerol content, both in the free and the triglyceride states. Now, there is no question as to the validity of the observations. They're comprehensive and clear-cut.

I would like to raise two interrelated points. One, how are the data to be interpreted in terms of overall mechanism?

And, two, how applicable are the observations to the clinical conditions where parenteral therapy is employed to prevent or treat protein-calorie malnutrition?

In regard to the first point, Brennan and his associates have made a number of relevant measurements in their comprehensive study. I would like to ask Dr. Brennan what the oxygen consumptions of the two groups of patients were. I ask this for the following reason:

The RQ's of the two groups were similar at about 0.65–0.70 suggesting that similar metabolic fuels were being metabolized by both groups of subjects.

If the oxygen consumptions of the two groups were similar, one might then conclude that the caloric expenditures of both groups were similar; in one case, a large proportion of the calories required being derived from the infused fat, in the other, a similar proportion of calories coming from endogenous stores of fat.

Now, not supporting this possibility are the higher levels of blood ketones in patients receiving the IV fat infusions. In this regard I would like to ask Dr. Brennan whether the reported values were from blood samples taken in the morning before the IV fat infusions, or later in the day during or after the IV fat infusions?

In support of the possibility that I mentioned is the approximately 1.2 kg greater average weight loss of the patients receiving the glycerol infusions.

Since the loss of lean body mass was presumably similar in both groups (the losses of urinary nitrogen were similar), it is likely that a large part of this difference in weight loss by the glycerol infused group represented body fat. If so, a rough calculation shows that its caloric potential is essentially the same as the amount of fat infused in the group receiving the 1.0 fat emulsion.

If the interpretation I've mentioned is valid, it would suggest that in the treatment of malnourished patients with depleted fat stores, the finding regarding protein sparing by the infused glycerol as opposed to the IV fat emulsion would likely be different from that observed in normal subjects or in patients with adequate fat stores. The last includes seriously ill and injured patients in the early period after injury. The first (i.e. patients with depleted fat stores) includes such patients late in their course. Of course, if the oxygen consumptions are substantially different in the two groups of patients, then the above considerations may not be applicable.

I would like also to ask Dr. Brennan about the sensitivity of the experimental model he and his associates have used. Specifically, is the magnitude of protein sparing produced by the glycerol close enough to the maximum possible that it's just not possible to show much difference?

I ask this because the protein sparing effect of i.v. glucose given in larger amounts than the i.v. glycerol, albeit in a study carried out earlier by Brennan and his colleagues, showed essentially the same protein sparing as that observed with the lesser amounts of glycerol.

DR. STANLEY J. DUDRICK (Houston): I assume from this paper that the authors are implying that the vast majority or indeed all of the protein sparing effects of the fat emulsions are a result of a glycerol and not the fatty acid or phospholipid components.

Do they mean to imply this or do they really mean that once the caloric equivalent of their infused gylcerol is reached by infusing the fat emulsion, no additional sparing was possible beyond that caloric value regardless of whether the extra calories were provided by fatty acids, phospholipids and/or glycerol?

If the latter, what do they propose is the role and fate of the infused fatty acids and phospholipids in their patients?

My second comment is these studies were performed in normal, healthy volunteers who apparently had good fat stores and were receiving no exogenous nitrogen. Have you studied subjects who have simultaneously received amino acids with these glycerol and fat emulsion infusions?

Have you studied or proposed to study patients with cachexia, trauma, sepsis, diabetes, renal failure or liver failure with and without exogenous nitrogen to try to define the truly clinically significant aspects of this work?

In other words, will you put it all together now you've shown us one important finding to see what the best possible combination might be for getting the patients who are nutritionally depleted well clinically?

The other question I have regards the statements at the beginning of the paper: "Serum samples were cleared of the turbidity present in the latter days of the lipid infusion by proceeding as for saponification but without addition of heat."

Does this imply that as you got perhaps toward the sixth, seventh or eighth day of your infusions, that you did have increased turbidity in your samples? If so, does this imply that the fat dose you were given couldn't be utilized over the long range as effectively later on at a higher dose as it could be earlier at the lower dose?

We've done some work in our laboratories, largely the work of Dr. Bruce McFabian in which he has shown that if you give the same dose of fat that you have given and then sequentially increase the non-fat calories as glucose that you have significant differences in utilization of the fat with each 1000 c of sugar that you give, so you can clear the fat from the serum about twice as fast with 3000 c of additional glucose as you can when you just give the fat alone or with 1000 c of exogenous glucose.

These are all very interesting and fascinating interrelationships.

DR. BASIL A. PRUITT, JR. (San Antonio): Sometime past we reported that Intralipid was not only safe but was effective in preventing or correcting essential fatty acid deficiencies. We have studied further its protein sparing effectiveness. In these studies carried out principally by Dr. Long of our laboratory, five patients, as identified here, received an isonitrogenous diet with varying caloric loads according to a randomized complete block design. Examining nitrogen excretion, as depicted here, I think you can see that there is no significant amelioration with increasing proportions of fat in the total caloric load. Nitrogen excretion appears to depend upon the carbohydrate calories provided.

This can be expressed as a curve where the total nitrogen excreted plateaus when the carbohydrate calories/metabolic rate ratio approaches one. The provision of additional calories does not modify nitrogen excretion.

The next slide shows a mathematical expression which can be derived from this where nitrogen excretion is a function of the carbohydrate intake and metabolic rate.

Further studies have shown that nitrogen excretion can also be expressed as a complex function of the nitrogen intake, carbohydrate calories, metabolic rate and basal insulin levels. (Slide) Applying that information to the same study format, you can see that provision of additional insulin marked by asterisks further increases nitrogen sparing. I would like to ask Dr. Brennan and his colleagues whether the insulin levels in the glycerol supplied patients were higher as a possible cause for the increased nitrogen sparing in that group?

DR. GEORGE H. A. CLOWES, JR. (Cambridge, Mass.): This is a fascinating phenomenon. I think Dr. Levenson gave us some suggestions as to why it might be occurring. I rise simply to state that I hope no one will go out of this room thinking that what we've heard is applicable necessarily to the clinical patient who is in a septic state.

From experimental and clinical observations, both in vivo and in vitro, we have good evidence that a muscle insulin resistance exists in the septic patient which does not of course exist in the starved patient.

Therefore, it's not surprising that the equivalent amount of glycerol or glucose would produce protein sparing in the normal starved individual, but that same amount of glucose if given by itself to the septic individual may make the situation worse in terms of negative nitrogen balance. The blood insulin level is raised by glucose. Blood from fatty acid is reduced by suppression of lipolysis, and the fuel deficit in the muscle then becomes considerably worse. All that remains for the muscle to do is to burn its branch chain amino acids (leucine, isoleucine, and valine). The rest of the amino acids must be transported to the liver where alanine and the glucose precursors are converted to glucose. It will be interesting to observe how glycerol infusion into septic patients affects sparing of their protein.

DR. HARRY LE VEEN (Brooklyn, New York): I rise only to make a philosophical point. Dr. Brennan mentioned the Gamble's famous life raft rations experiments which were done in World War II to find out how to keep people alive with the least amount of food. Ever since that time, unfortunately, our present concepts are strongly influenced by the past.

Now, during starvation there is at first a considerable nitrogen loss which settles down to become a small daily loss primarily from mobilized muscle mass. There is little evidence to support the concept that this small loss of muscle mass is in any way lethal. Yet, surgeons have been preoccupied with nitrogen balance.

Really what they should be preoccupied with is fat stores, because if starvation continues, there is a premortal rise in nitrogen output. This premortal rise corresponds to the point when body fat runs out and then there's this premortal rise in nitrogen output.

Since Gamble's time, we've heard from surgeons that it is not necessary to give over 5% or at maximum 200 gm of glucose a day; you can't spare any more protein with giving any more glucose.

But you can spare fat and you can put off to that fatal day when you run out of fat and you have this premortal rise. I think that the preoccupation with nitrogen balance in the early days of starvation is not exactly what we should be focusing our attention on.

DR. MURRAY F. BRENNAN (Closing discussion): I shall try to cover what points I can and just acknowledge that a lot of new areas are opened to examination.

Dr. Levenson's interpretation does confirm what data we have. Oxygen consumption is similar in both groups. We do believe this is a reflection that the people receiving low quantity of substrate, that is, the glycerol group, are living off their own endogenous fat. I think, to some extent, this is confirmed by their weight loss.

His question about ketone bodies, yes, they were certainly elevated at the time of infusion. They were certainly more elevated at the latter part of the study. We tried very hard to try to catch this in two places by measuring at 8 a.m. and two in the afternoon, the latter of course coinciding with infusion time. However, as Dr. Dudrick alluded to, on the last two or three days, there was incomplete clearing and I'll mention that when I answer Dr. Dudrick's comments.

Dr. Levenson very provocatively asked if we were advocating glycerol as an appropriate substrate. My only comment can be that we have no data to suggest that. You can say that it is not an insulin needing carbohydrate.

Dr. Dudrick's very incisive comments have a particular point to make, and it should be made in prefix to all our comments; we are talking about sparing nitrogen in the absence of nitrogen intake and that is entirely different from the person who is provided with nitrogen. There is a certain intake of nitrogen (moderately well worked out in the rat) above which no matter what way you give energy or calories there will be nitrogen sparing, and a level of nitrogen intake below which fat is much less advantageous than carbohydrate.

The clinical studies, Dr. Dudrick, have not been done. We look forward to the opportunity to do them.

Your comment about the question of methodology is correct. The turbidity on the last two or three days of 3gm/kg/day of intralipid indicates that normal man does not clear that dose. Again, it is without other substrate. I think your own nice work with Dr. McFadyean shows that if you give people other carbon chains they will clear fat more rapidly. That has been the experience in Scandinavia and Europe where as much as 12 gm/kg/day have been given without reported side effects.

Dr. Pruitt, we have enjoyed the work of Drs. Long, Wolmar and yourself and I think it confirms the concept put forth by Cathcart that "isotameutic" is not equal to "isodynamic." That is to say, quality of nitrogen sparing is not the same as the quality of energy availability.

It is interesting, Dr. Pruitt, that the insulin levels under both these regimens do not change. They don't rise and they fall insignificantly. For an absolute level, for what that's worth, it was 20 to 15μU/ml in our studies.

Dr. Clowes, we have no evidence that this is what you should be doing to the patient in sepsis. We have not studied that and it would be grossly premature of me to comment. We certainly aren't saying that you should go home and infuse patients with glycerol.

Dr. Le Veen, we would agree that a small loss of muscle mass is of little significance. The repairing of an inguinal hernia and the subsequent loss of 5 or 6 gm of nitrogen a day, to my knowledge, has never been shown to be deleterious. There is no question, however, as Dr. Kinney, has so clearly pointed out, that percentage weight loss is paralleled by percentage loss of lean tissue, and there has to be an end at which available protein is self-limiting. In our experience, that's often in the sick patient long before their fat stores are exhausted. Most of us have at least 140,000 calories sitting as fat when we present after our first motor vehicle accident.

If I can summarize then and apologize for those comments that I have not answered, 75 years before this hotel was built, Dr. Magendie studied a similar subject: "the effects of substrates without the presence of nitrogen."

At that time he raised some questions that went unanswered. My only defense to those questions I have not covered is paralleled by Dr. Magendie's answer to his critics. To those questions we have not answered, we will try to complete the appropriate experiments.

Body Composition in Morbidly Obese Patients Before and After Jejunoileal Bypass

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A clinical and body compositional study has been made of 150 patients with morbid obesity and their responses to four different dimensional alterations of jejunoileal bypass. Total body potassium was estimated by measuring ^{40}K with the whole body counter and total body water by tritiated water dilution. Body compositional data derived from these measurements were compared in the 4 groups during followup periods up to 4 years and related to clinical results. Initially, patients were two or more times overweight due to excess (60 to 65%) body fat and increased hydration (21%) of lean tissues. The 80 end-to-end jejunoileal bypass procedures of Groups 3 and 4 (30 cm jejunum to 15 or 20 cm ileum) had better weight losses and clinical results in followup were rated "good" in 60% and 81% respectively. These results were accompanied by a greater degree of improvement in body composition than was observed in the other groups under study.

DURING THE PAST 9 years we have conducted a clinical and metabolic investigation of morbid obesity and the role of jejunoileal bypass in surgical management.[8–10] Over 150 patients have been selected for operation out of a much larger group after extensive in-hospital appraisal according to the criteria in Table 1.

In addition to clinical and metabolic assessment of these patients and their responses to operative treatment we have studied their body composition before and at intervals up to 4 years after jejunoileal bypass.[2] Total body potassium has been estimated by measuring ^{40}K with the whole body counter.[3] Total body water space has been measured by isotope dilutional methods using tritiated water (T_2O).[5] Two types of estimate of the fat free lean body moiety (the body cell mass of Moore et al.[4]) have been made: (1) lean body mass (LBM) from ^{40}K whole body counting and (2) fat free body (FFB) from T_2O body water space. Body fat content is estimated as the difference between these measurements and body weight.

Follow-up clinical data after 4 different dimensional alterations of jejunoileal bypass have been obtained from one to 8 years in over 100 obese patients. In this report the body compositional alterations in these groups of patients are compared and analyzed for periods extending up to 4 years. These data provide additional parameters in assessment of the morbidly obese patients' result from surgical treatment.

Methods

The end-to-side jejunoileal shunt described by Payne and DeWind[6] was used in the first 11 patients (Group 1). Although Payne[7] has continued to report acceptable weight loss with this type of jejunoileal bypass, our experience was disappointing.

Because of dissatisfaction with the results of Payne's procedure, we have used a different principle of

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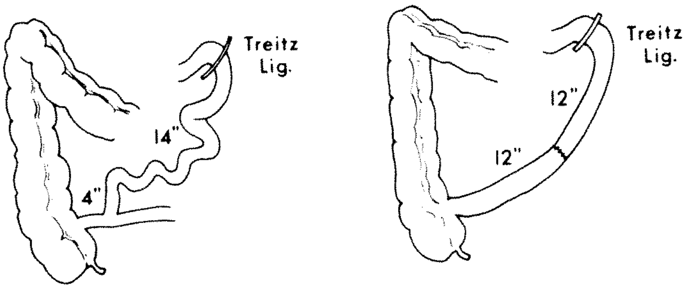
TABLE 1. *Criteria for Selection of Patients for Jejunoileal Bypass*

1. Obesity of massive degree (weights of 2 to 3 times ideal levels) of at least 5 years' duration.
2. Evidence from the attending physician indicating failure of dietary efforts to correct obesity over a period of years.
3. Evidence from the patient's history and evaluation indicating incapability to adhere to prescribed dietary regimen and/or exercise programs.
4. Absence of any correctable endocrinopathy (such as hypothyroidism or Cushing's syndrome) which might be the cause of obesity.
5. Absence of any other unrelated significant disease which might increase operative risk.
6. Presence of certain complications such as Pickwickian syndrome, hyperlipidemia, adult onset of diabetes, and hypertension which might be alleviated by significant weight reduction.
7. Assurance of patient's cooperation in conduct of pre and postoperative metabolic and body compositional studies and prolonged followup evaluation.

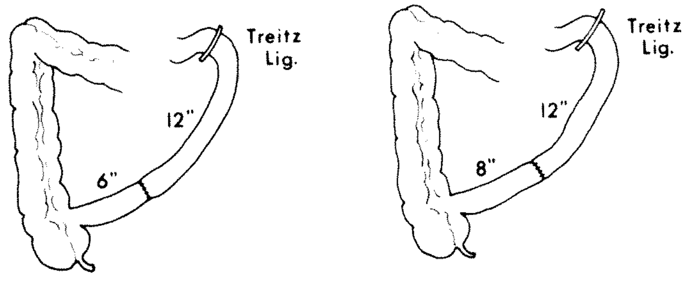
jejunoileal bypass in the subsequent patients. Following the new principle, the jejunum is divided a few inches from the ligament of Treitz and its proximal end anastomosed to the distal end of transected ileum a few inches proximal to the ileocecal valve. The long length of bypassed jejunoileum is drained by anastomosis of its proximal ileal end to transverse colon or sigmoid.[9]

In an effort to determine the optimal dimensions of the shortened bowel in the end-to-end method of the jejunoileal bypass procedure the following plan has been followed in these patients: In 12 patients (Group 2) 12 inches of proximal jejunum were joined by end-to-end anastomosis to the distal 12 inches of ileum (30 cm to 30 cm). In Group 3 in 21 patients the proximal 12 inches of jejunum were joined to ileum 6 inches proximal to the ileocecal valve (30 cm to 15 cm). In Group 4 in over 100 patients the anastomosis of proximal jejunum 12 inches from Treitz ligament was made to ileum 8 inches from the ileocecal valve (30 cm to 20 cm) (Fig. 1).



Payne's Operation (Group 1)

(Group 2)



(Group 3)

(Group 4)

FIG. 1. Diagrams of the four dimensional variations of jejunoileal bypass used in this study.

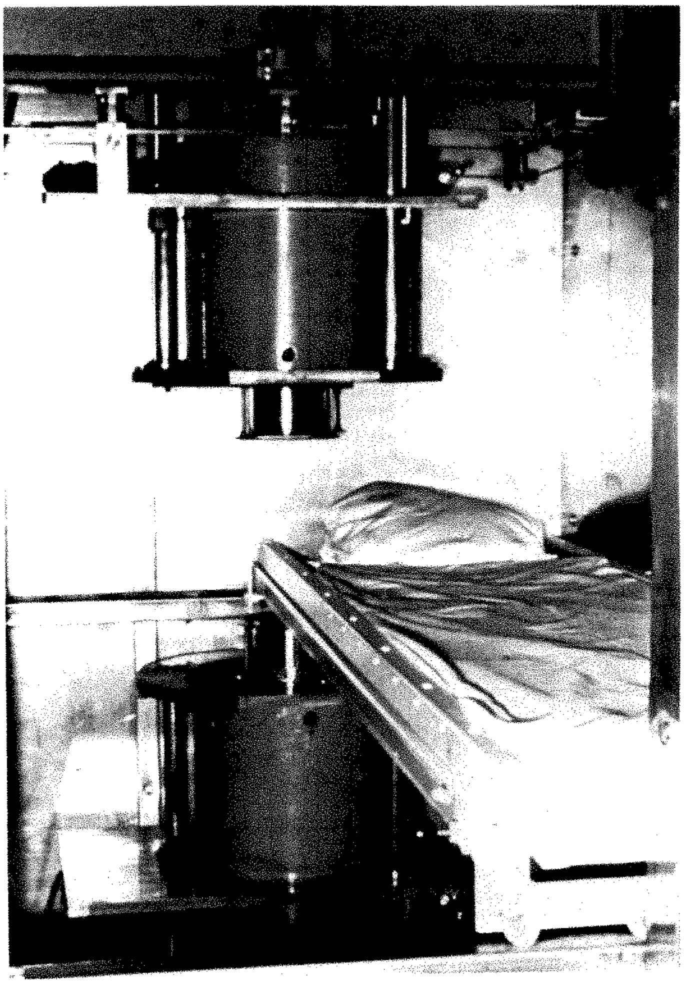


FIG. 2. ^{40}K whole body counting system used in this study.

In addition to clinical and metabolic appraisal, lean body mass (LBM) was measured before and at intervals after jejunoileal bypass in the majority of these obese subjects.

Potassium is primarily localized intracellularly and the potassium content of fat is very low. The naturally occurring radioactive isotope of potassium ^{40}K is equivalent to .01 per cent of naturally occurring potassium and can be measured by very sensitive, well shielded counters. The measurement system we use for these studies is shown in Fig. 2. The patient lies on the bed and radioactive emanations are counted for 30 minutes. The system is calibrated with known amounts of ^{40}K so that counts per minute from the patient can be translated directly into milliequivalents of potassium and lean body mass (LBM in kg =

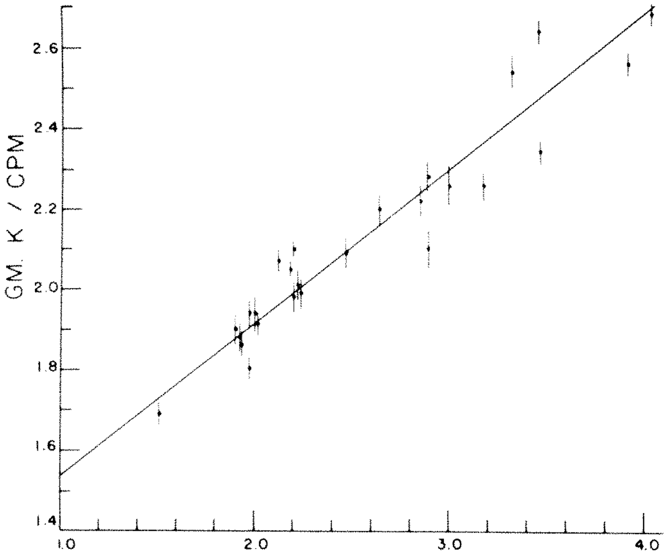


FIG. 3. ^{40}K whole body counter calibration curve.

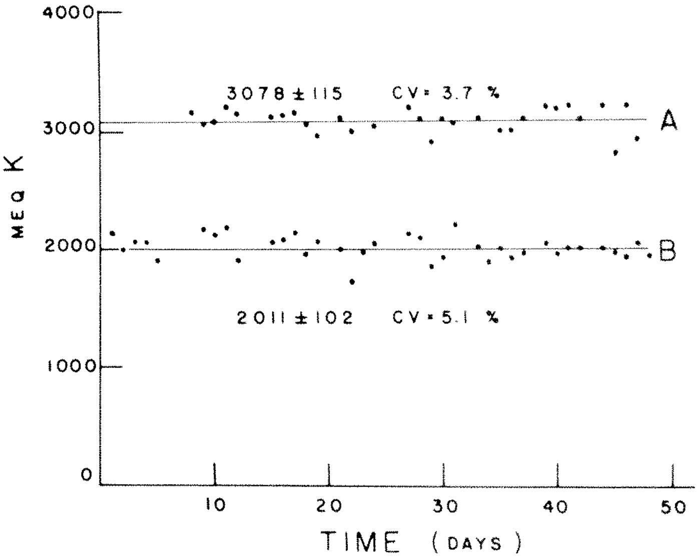


FIG. 4. Daily measurements of whole body potassium in two normal subjects recorded over a 7-week period.

mEq of K/68.1). The calibration curve is shown in Fig. 3. The calibration factor is plotted against weight/height and is well represented by a straight line. (Least squares best fit, $Y = 0.3769 \times + 1.16$). The variability between subjects with the same weight/height ratio is usually small. Calibration factors were established for each patient at each time his ^{40}K was determined initially. In later studies, we used the calibration curve established for the range of weights in the early study groups.[3]

In order to establish the reproducibility of the technique, daily measurements were made in a small series of normal subjects. The data of two such subjects are shown in Fig. 4. For subject A the co-efficient of variation was 3.7% as opposed to 5.1% for subject B. This indicates that 67% of the time that ^{40}K was determined in subject A, the value was within 3.7% of the mean, and that in 95% of the cases it was within 7.4% of the mean.

Tritiated water space (TWB) has been determined in many of the subjects in this study. Samples taken between 4 and 6 hours after oral administration of 75 μCi of T_2O are assayed in a liquid scintillation counter, urine losses are measured, and the size of the total body water space is computed using standard isotope dilution technics. In some patients TBW was measured repeatedly out to 5 days.[2,5]

The TBW measurements can be translated directly into the mass of the fat free body (FFB in kg = TBW in liters/0.732). In normal subjects, 73.2% of the LBM is equal to the TBW content. The factor .732, however, is not necessarily valid for various disease states. In a selected number of massively obese patients of this study, the factor we established was 0.888, which corresponds to a 21.3 ± 12.4% increase in total body water above that predicted for a normal person with the same lean body mass.[2,5]

Clinical Appraisal of Patients

One hundred and fifty massively obese patients who were selected by the criteria in Table 1 were submitted to jejunoileal bypass during the period 1966 to 1975. Ages ranged from 16 to 63 years (average 36 years). There were 87 women and 63 men. There was a long history (5 to 10 years or more) of massive obesity refractory to dietary control in each instance. Maximal weights prior to operation ranged from 280 to 600 pounds (127 to 272 kg). Immediately before operation weights ranged from 240 to 560 pounds (109 to 255 kg.). One patient had been submitted to the Payne operation three and one half years previously but had failed to drop her weight below 260 pounds.

Each patient was admitted to the hospital for study prior to operation. Baseline studies were carried out with special attention directed toward detecting possible endocrine causes of obesity, evaluation of cardiopulmonary status, baseline absorptive and metabolic studies, psychiatric and psychologic evaluation and isotopic measurement of body composition.

Preoperative clinical evaluation of the 150 patients in this study showed a variety of abnormalities in addition to massive obesity. A family history of obesity in individual parents, grandparents or siblings was elicited in about half of the patients. Twenty-seven patients had gallstones and 15 others had had previous cholecystectomy. Forty-two patients had glycosuria and diabetes positive glucose tolerance tests. Endocrine status was otherwise normal by our appraisal.

Cardiac evaluation before operation showed 22 patients to have diastolic hypertension in the range of 110 to

TABLE 2. *Body Weight (kg)*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon
1	173.59 ± 40.8 (7)*	139.55 ± 52.57 (4)	112.49 ± 15.16 (9)	118.47 ± 38.78 (7)	121.56 ± 30.62 (7)
2	141.91 ± 26.15 (10)	136.29 ± 36.1 (8)	105.39 ± 24.04 (8)	107.02 ± 12.85 (4)	96.91 ± 10.09 (8)
3	153.2 ± 32.14 (20)	110.8 ± 17.14 (6)	104.45 ± 21.57 (13)	97.13 ± 19.25 (4)	91.7 ± 21.57 (11)
4	142.22 ± 27.36 (49)	123.92 ± 22.3 (18)	103.64 ± 14.54 (21)	94.94 ± 13.63 (14)	86.78 ± 14.22 (9)

*No. patients in each study period are in parentheses.

130 mm Hg. One patient had sustained a previous stroke and two had had previous myocardial infarction.

Sixty-eight patients had hyperlipidemia as exhibited by abnormal elevation of serum cholesterol and/or triglyceride concentrations along with abnormal lipoprotein electrophoretograms. Twelve of these patients had Frederickson's Type II hyperlipoproteinemia, while 55 patients had Type IV and one had Type V.

Preoperative appraisal of intestinal fat, carbohydrate and nitrogen absorption was normal in each patient prior to operation except in one woman who had had a previous Payne procedure with attendant elevation in fecal fat losses. Measurements of serum vitamin levels, electrolytes and hematologic functions prior to operation in these obese patients showed no significant abnormalities.

In the majority of patients, recovery from operation was uneventful. However, there were 5 postoperative deaths in the series of 150 patients: one with bowel infarction from mesenteric venous thrombosis after intestinal bypass and extensive ileal and mesenteric resection for a malignant ileal carcinoid with nodal metastases to the root of the mesentery; three from pulmonary embolism; and a fifth from diffuse thrombophlebitis, hemorrhagic pneumonia and sepsis. The operative mortality rate was 3%.

Non-fatal postoperative complications developed in 31 patients. These included wound seroma in 13 patients and superficial wound infection in 14 others. One of these also developed stomal obstruction, which required revision, and venous thrombosis with pulmonary emboli. One other patient had thromboembolic complications. Two patients developed early postoperative hepatitis, due we believe, to halothane anesthesia. There was one early (first day) evisceration. All patients with these complications recovered with appropriate treatment.

Nasogastric suction was discontinued two to three days after operation and oral liquids, usually restricted to 1500 ml daily, were started. In the first few days after institution of oral liquids multiple watery stools occurred. Low fat diet, restriction of fluids with meals and diphenoxylate hydrochloride in a dosage of 5 mg 3 to 4 times a day or codeine 15 to 30 mg 3 to 4 times a day usually resulted in satisfactory control of the diarrhea during the early postoperative period.

After discharge from the hospital each patient has been followed in conjunction with the family physician and in our clinic. An effort has been made to have all patients return repeatedly for both outpatient and inpatient studies of their clinical result, nutritional, metabolic and body compositional status, psychiatric state and degree of rehabilitation. Details of the nutritional, metabolic and psychiatric results have been reported separately and exceed the scope of this report.[2,8,10]

Results

Periods of followup in the groups under study range from 5 to 8 years in the patients with Payne's operation (Group 1) and from 3 to 4 years in the patients of Group 2, from 2 to 3 years in the patients of Group 3 and up to 2 years in the patients with the 12″ to 8″ jejunoileal shunt of

TABLE 3. *Total Body Potassium (mEq K)*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon
1	4298.57 ± 894.0 (7)*	3865.75 ± 1659.6 (4)	3222.67 ± 458.36 (9)	3718.86 ± 961.7 (7)	3498.0 ± 983.1 (7)
2	3683.2 ± 1672.55 (10)	3542.0 ± 1028.09 (8)	3103.87 ± 611.65 (8)	3811.5 ± 989.27 (4)	3040.12 ± 805.68 (8)
3	4304.18 ± 1165.35 (20)	2720.17 ± 635.0 (6)	3231.23 ± 1059.54 (13)	2935.0 ± 630.97 (4)	3319.18 ± 877.98 (11)
4	3691.69 ± 689.11 (49)	3346.0 ± 981.43 (18)	2935.62 ± 943.51 (21)	3125.14 ± 564.17 (14)	2935.22 ± 909.82 (9)

*No. patients in each study period are in parentheses.

TABLE 4. *Total Body Water (Liters)*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon
1	55.70 ± 10.23 (5)*	36.0 ± 0 (1)	47.99 ± 6.55 (7)	46.08 ± 13.44 (5)	47.77 ± 6.10 (3)
2	53.91 ± 6.17 (5)	48.3 ± 0 (1)	35.34 ± 4.27 (2)	49.32 ± 0 (1)	25.98 ± 0 (1)
3	56.57 ± 10.47 (3)	56.59 ± 0 (1)	—	56.04 ± 0 (1)	40.67 ± 13.71 (4)
4	44.60 ± 12.26 (18)	44.24 ± 14.95 (9)	39.73 ± 13.33 (8)	44.44 ± 9.70 (9)	40.54 ± 6.83 (5)

*No. patients in each study period are in parentheses.

Group 4. The data detailing weight loss after jejunoileal bypass in the patients of these several groups are presented in Table 2.

Although early precipitant weight loss occurred in each group, those with Payne's operation (Group 1) and 50% of those with 12″ to 12″ end-to-end jujunoileal shunt (Group 2) subsequently lost weight more gradually and their weights tended to plateau after 12 to 18 months at levels above ideal range. After two or more years a few patients in both of these groups had begun to regain weight. In contrast, patients in the groups of end-to-end jejunoileal shunt with 12 inches of jejunum joined to 6 or 8 inches of distal ileum (Groups 3 and 4) have had a more rapid rate of weight loss during the first year after operation. More than 70% of patients in these two groups followed for one year or more have achieved reductions to the range of ideal weight.

Tables 2, 3 and 4 summarize the measurements of body weight (Wt), total body potassium (mEq K) and total body water (TBW) for patients belonging to each of the four operative groups. The tables present the means and standard deviations of the observations as calculated for each group prior to the operation and at 4 time intervals (extending up to 40 months) after operation.

None of the patients in the four groups failed to lose weight; however, the degree to which this weight loss resulted in improved body composition can be better assessed by analysis of the derived quantities of the lean body mass/body weight (LBM/kg) and the fat free body/body weight (FFB/kg). These quantities, although arrived at by completely independent measurements, are both a measure of the fraction of the total body which contains no fat. We will reserve the symbols (LBM/kg) to correspond to the quantity derived from the measurement of total body potassium using the whole body counter and the symbols (FFB/kg) to correspond to the measurements of whole body water using isotope dilution measurements of T_2O.

Tables 5A and B show the results of the LBM/kg for each operative group calculated at the same time intervals as described previously. The entries are the group means of the fraction of the total body which does not contain fat. For reference a normal healthy male may have values of LBM/kg or FFB/kg ranging from 0.65-

TABLE 5A. *Lean Body Mass (kg)*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon
1	63.11 ± 13.14 (7)*	56.37 ± 24.98 (4)	47.30 ± 6.73 (9)	54.60 ± 14.12 (7)	51.37 ± 14.45 (7)
2	55.72 ± 8.50 (5)	52.10 ± 15.12 (8)	45.59 ± 8.99 (8)	55.97 ± 14.54 (4)	44.64 ± 11.82 (8)
3	63.2 ± 17.12 (20)	39.93 ± 9.33 (6)	47.45 ± 15.56 (13)	43.10 ± 9.26 (4)	48.73 ± 12.90 (11)
4	54.21 ± 10.11 (18)	49.16 ± 14.41 (18)	43.10 ± 8.29 (14)	45.89 ± 8.29 (14)	43.09 ± 13.37 (9)

*No. patients in each study period are in parentheses.

TABLE 5B. *LBM/Weight*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon	% change from initial at 18-40 mon
1	.35	.32	.41	.40	.42	+20.0%
2	.40	.39	.44	.53	.47	+17.5%
3	.41	.36	.45	.44	.54	+31.7%
4	.38	.40	.45	.49	.50	+31.6%

TABLE 6A. *Fat Free Body/kg Body Weight (Conversion Factor = 0.89)*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon	% change from initial at 18-40 mon
1	.34	—	.48	.43	.46	+21%
4 (all patients)	.34	.41	.45	.54	.55	+62%
4 (good results)	.34	.40	.45	.58	.59	+74%

0.80.[4] Although none of these groups achieved this level, most do show improvement as compared to the preoperative measurements. Since it is our presumption that it is the ultimate body composition that is most important to the patient's health, we have calculated the percentage change in the LBM/kg as measured before operation to the value as determined for the 18-40 month time interval. As shown in Tables 5A and B the value of this indicator of improved body composition was 20% for Group 1, 17.5% for Group 2, 31.7% for Group 3 and 31.6% for Group 4. The increase in the fraction of the body which was lean was found to be statistically significant ($P<0.01$) for Groups 1, 2. 3, and 4.

Tables 6 A to C show the group mean values for the FFB/kg for patients in Groups 1 and 4. There were inadequate numbers of studies in Groups 2 and 3 for analysis and these were not included in these tables. Paralleling the analysis of the LBM/kg we calculated the percentage change at the 18-40 month interval with respect to initial value. The group with Payne-DeWind operation (Group 1) was found to have an increase of 21%. Group 4 showed an increase of 62%. Both results were found to be statistically significant ($P<0.01$) increases and Group 4 showed a statistically significant increase over Group 1.

In normal subjects 73.2% of the fat free body (FFB) is equal to the TBW content.[4] However, as previously stated the factor .732 is not necessarily valid for various disease states. As we have reported previously[2] we have established the factor to be 0.888 in a group of our massively obese patients. For these reasons we have included entries for FFB/kg using both conversion factors ($f=.732$ and $.888$) in Tables 6A to C. The corresponding measurements of LBM/kg are also included in Tables 6A to C for comparison. In comparing the FFB/kg to the LBM/kg, it is obvious that the quantities derived using $f=0.888$ are more consistent with the values for LBM/kg than are those with $f=.732$.

The fact that absolute values of the percentage change are generally much higher for the FFB/kg than for the LBM/kg leads one to postulate that f may not be a constant throughout the observation period for each group. However, our data are not adequate to establish this.

During the followup period of a few months to 8 years, there have been 5 deaths among the 145 patients who have survived jejunoileal shunt. The results of clinical followup based on the criteria listed in Table 7 have been appraised critically in all surviving patients in each group who have been followed for one year or more after jejunoileal bypass.

The results of this appraisal are summarized in Table 8. In the 11 patients with end-to-side jejunoileal shunt (Group I) followed 5 to 8 years, the absence of good results and the predominance of poor results reflect the failure of satisfactory sustained weight reduction.

In the 92 patients with end-to-end jejunoileal shunt who have been followed from one to 4 years, the results have varied with the dimensions of shortening of the intestine used at operation.

In Group 2 (30 cm to 30 cm) 6 of the 12 patients (50%) achieved a good result. Fair results which were achieved by 5 of this group were due to failure to reach and maintain truly satisfactory weight reduction to the ideal range. No significant metabolic or nutritional deficits have developed in any of this group of patients and diarrhea has not persisted as a problem. One patient had a poor result because of totally inadequate weight loss.

Among the 80 patients in Groups 3 (30 cm to 15 cm) and 4 (30 cm to 20 cm) who have been followed one to 3 years, 61 (75%) have achieved a good result. Good results have been obtained by 81% of the 60 patients in Group 4 who have had followups of one to two years.

The degree of rehabilitation in the patients who have had good results and most of those who are credited with fair results is difficult to measure objectively. Return to

TABLE 6B. *Fat Free Body/kg Body Weight (Conversion Factor = .732)*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon	% change from initial at 18-40 mon
1	.47	.42	.59	.53	.57	+21%
4 (all patients)	.42	.51	.56	.66	.68	+62%
4 (good results)	.42	.49	.55	.71	.73	+74%

TABLE 6C. *LBM/Weight*

Group	Initial	0-6 mon	6-12 mon	12-18 mon	18-40 mon	% change from initial at 18-40 mon
1	.35	.32	.41	.40	.42	+20.0%
4 (all patients)	.38	.40	.45	.49	.50	+31.6%
4 (good results)	.40	.42	.44	.51	.53	+33.0%

full preoperative work capacity or assumption of full-time or part-time new work has been accomplished by all but 6 patients. In the latter small group retirement programs or wealth which precluded the need to work have been important influences. The new body image developed by those individuals who have brought their massively overweight status down to a normal or near normal weight range has been impressive to our medical and surgical team and in particular to our clinical psychologists and psychiatric consultants. A study of personality profiles and psychologic aspects of the massively obese patients of this group before and after jejunoileal bypass will be reported separately.[1,11]

In addition to the 5 patients who died during the period of followup there were 4 other patients in Groups 3 and 4 who were credited with poor results. One of these in Group 3, a 31-year-old man who had serious emotional problems and who lost 100 pounds in 6 months after jejunoileal bypass, developed severe anxiety, weakness, diarrhea and electrolyte deficits. These were the principal reasons for take-down of his jejunoileal shunt by his local surgeon 9 months after the initial procedure. The other three patients with poor results during followup were in Group 4: one patient failed to lose weight satisfactorily and currently two years after operation remains massively obese despite the shortened bowel. The second patient, whose weight is satisfactory two years after operation, has had persistent watery diarrhea and inadequate followup. The third patient had recurrence of a previously healed duodenal ulcer associated with abdominal pain, vomiting, persistent diarrhea, hypokalemia and recurrent pulmonary emboli which necessitated treatment by vagotomy, pyloroplasty, take-down of the jejunoileal shunt and a clip on the vena cava. In the 6 months since this procedure he has been quite well.

TABLE 7. *Criteria in Appraisal of Results*

Good	Weight loss satisfactory No diarrhea problem No metabolic deficits
Fair	Weight loss not ideal Mild diarrhea on occasion Minimal metabolic deficits
Poor	Weight loss unsatisfactory Persistent diarrhea Severe metabolic deficits

In an effort to assess the relationship of the clinical followup evaluation to alterations in body composition in patients after jejunoileal bypass two pertinent questions have been raised: (1) Is the end-to-end type of jejunoileal bypass procedure more effective in bringing about improved body composition than the Payne-DeWind operation? (2) Is an improved body composition reflected in the clinical assessment of the patient?

Figures 5 and 6 show the graphical representation of the numbers presented in Table 6 for the LBM/kg and the FFB/kg for Group 1 and Group 4. In each case it can be seen that the 30 cm to 20 cm end-to-end jejunoileal bypass operation of Group 4 results in a monotonic increase in the LBM/kg and in the FFB/kg and in each case attained a statistically higher fraction that did the Payne operation of Group 1 ($P<0.05$ for LBM/kg and $P<0.01$ for FFB/kg).

In further appraisal of the relationship of the body composition to the clinical result, we have recalculated the LBM/kg and the FFB/kg from the data of those patients of Group 4 which were evaluated as "good." The results of these recalculations are shown in Table 6 and in Figs. 5 and 6. In each case (LBM/kg and FFB/kg) the

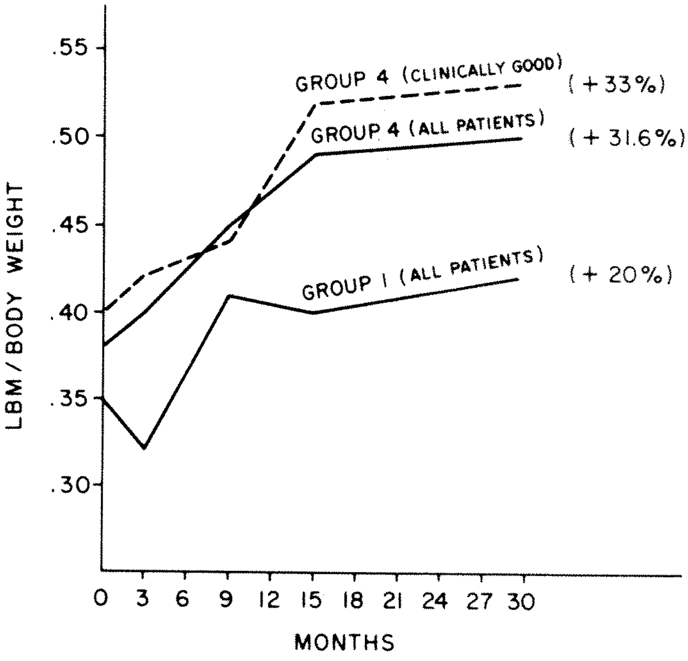


FIG. 5. Lean body mass as fraction of body weight (LBM/Wt.) plotted against time.

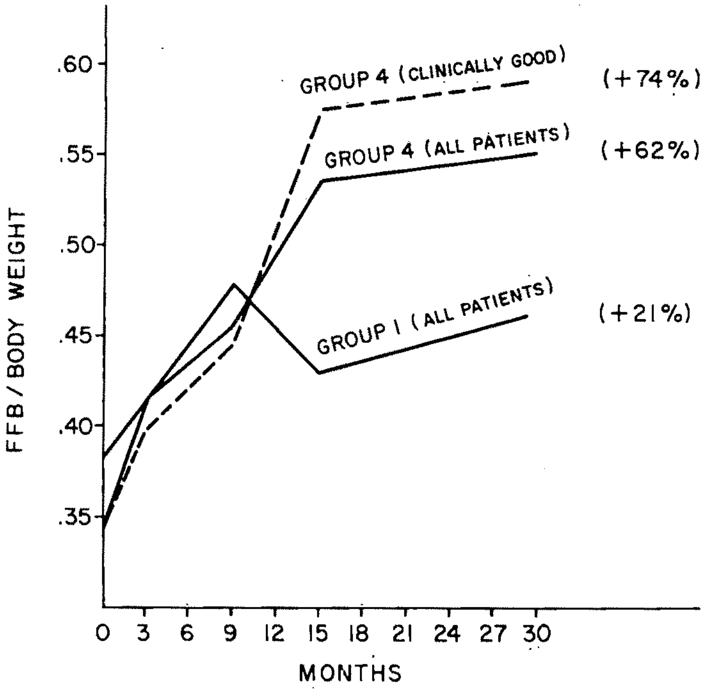


FIG. 6. Fat free body as fraction of body weight (FFB/Wt.) plotted against time.

level of improvement in the body composition was increased (31.6 to 33%) for the LBM/kg and (62 to 74%) for the FFB/kg. Since the two populations in Group 4 are nearly identical for both LBM/kg and for FFB/kg, it is not surprising that differences are not statistically significant.

Comments

In the classic work on body composition in health and disease Moore and his associates[4] have pointed out that the techniques of body composition should be able to provide information relative to two aspects of the obese patient: first, the extent of his obesity and second, the state of health of his remaining tissue, the fat free body.

The data in Tables 2, 3, 4, 5, indicate that initially the patients in this study were two or more times overweight, and the overweight was largely due to body fat content (60 to 65%) and increased hydration (21%) of the fat free lean tissues. These body compositional alterations fit Moore's concept of "unhealthy" obesity.

Figure 7 plots the changes in body weight as percentage of initial in the four groups (Fig. 1) of obese subjects. All groups sustained a 25 to 35% mean weight loss in the first year after jejunoileal bypass. Thereafter, Groups 3 and 4 continued to lose weight at a greater rate than Group 2 while in Group 1 over the next 18 months the patients began to regain weight. Thus, the end-to-end procedures of Groups 3 and 4 have yielded better weight losses which more closely approach ideal levels with no evidence of a reversal in the trend. The more desirable weight loss profile exhibited by Groups 3 and 4 was also accompanied by a more desirable body composition as estimated by two independent methods of measurement of the fat-free tissues (Tables 5 and 6).

TABLE 8A. *Jejunoileal Bypass for Morbid Obesity (1966-1975): Results of Followup*

End-to-Side Jejunoileal Shunt	No Patients	Yrs	Good	Results Fair	Poor
(Payne Procedure) 35 cm. to 10 cm. (Group 1)	11	5-8	0	2	9

In those groups where the fat-free fraction continues to increase (Tables 5, 6, and Figs. 5, 6) the fraction of the body which is fat must be decreasing. This implies that the loss of body fat must be proceeding at a greater rate than is the loss of the fat-free tissues.

With the two assumptions (1) that potassium is located primarily intracellularly and is not present in any appreciable quantities in fat and (2) that fat contains essentially no water, we have used the combined data from the whole body counting of radioactive potassium (^{40}K) and the measurements (T_2O) of total body water to estimate the degree of hydration of the fat free tissues in our morbidly obese patients. We have determined the preoperative hydration fraction to be 0.89 in these obese subjects rather than the accepted normal value of 0.732. This corresponds to a 21% increase in the total body water over that of normal subjects with the same amount of fat free tissues. Although suggesting that the hydration fraction tends toward the normal value in the period of postoperative followup, the data are not adequate to establish this. Further measurements will be required to answer this question.

TABLE 8B. *Jejunoileal Bypass for Morbid Obesity (1966-1975) Results of Followup*

End-to-End Jejunoileal Shunt	Patients	Yrs	Good	Results Fair	Poor
30 cm. to 30 cm. (Group 2)	12	3-4	6	5	1
30 cm to 15 cm. (Group 3)	20	2-3	12	7	1
30 cm. to 20 cm. (Group 4)	60	1-2	49	8	3

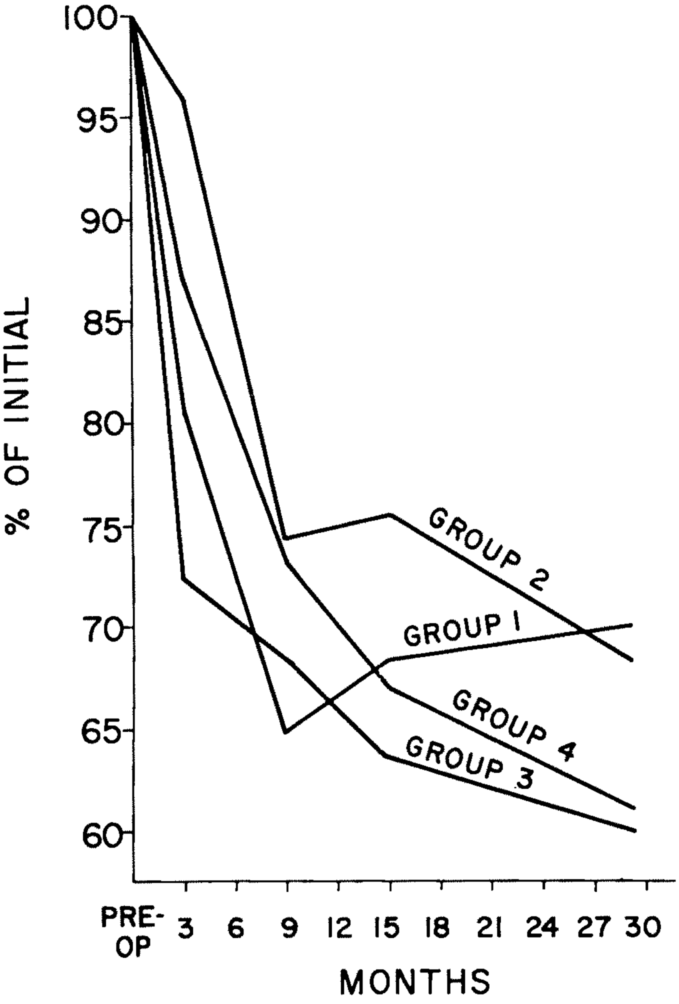


FIG. 7. Body weight as per cent of initial.

Clinical criteria were established in order that the patients' result could be graded "good," "fair" or "poor" on followup clinical evaluation (Table 7). Using these criteria, Groups 3 and 4 were found to present a much better clinical profile than did Groups 1 and 2. In Group 1 none of the patients presented "good" results on long-term followup evaluation. On the contrary Groups 2, 3 and 4 had, respectively, 50%, 60% and 81% of their patients evaluated as "good" (Table 8).

In order to assess the relationship between improved body composition and the clinical evaluation, the body composition profile of those patients rated "good" in Group 4 was determined (Table 6, Figs. 5, 6). The data suggest that the patients who received "good" clinical scores are more likely to attain an improved body composition; however, due to the small number of patients having "fair" and "poor" results this could not be verified statistically.

The degree to which improved body composition corresponds to improved physical fitness is an important additional question which deserves attention in the evaluation of these patients. This and other related questions are currently under consideration.

Summary

A clinical and body compositional study has been made of 150 patients with morbid obesity and their responses to four different dimensional alterations of jejunoileal bypass. Total body potassium was estimated by measuring ^{40}K with the whole body counter and total body water by tritiated water dilution. Body compositional data derived from these measurements were compared in the four groups during followup periods up to 4 years and related to clinical results. Initially, patients were two or more times overweight due to excess (60 to 65%) body fat and increased hydration (21%) of lean tissues. The 80 end-to-end jejunoileal bypass procedures of Groups 3 and 4 (30 cm jejunum to 15 or 20 cm ileum) had better weight losses and clinical results in followup were rated "good" in 60% and 81% respectively. These results were accompanied by a greater degree of improvement in body composition than was observed in the other groups under study.

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DISCUSSION

DR. JAMES ISAACS (Atlanta): I rise to present additional data which support Dr. Scott's finding that patients lose lean body mass after a jejunoileal bypass.

At Emory, Dr. William Millikan, Dr. Dean Warren, and Dr. Daniel Rudman studied 21 patients with jejunoileal bypass. Using balance studies, they documented the depletion of elements comprising the lean body mass in these subjects by a method independent from that used by Dr. Scott. In addition, they found three dietary methods to reverse this depletion. Their study will appear in print later this year.

(Slide) This demonstrates 3 diets fed to J-I bypass patients during balance studies. Diet "A" contained 80 gm of protein and 100 gm of fat: a normal diet. Diet "B" and "C" represent modifications of Diet "A". Diet "B" was simply diet "A" with half of the natural protein in Diet "A" replaced by an equivalent amount of elemental amino acids. Diet "C" was the same as diet "A" except it furnished 30 gm instead of 100 gm of fat.

This slide shows nitrogen absorption in 4 of 11 patients with stable body weight who were studied a year or more after bypass. Nitrogen absorption on Diet "A" ranged from 50% to 70%. When diets containing 30–80 gm of fat instead of 100 gm were eaten, nitrogen absorption increased by as much as 20%.

This slide shows nitrogen balances for 3 of 10 patients studied within 1 year of surgery. All 3 patients were in the acute phase of weight loss. In two patients, when a regular diet was eaten, Diet "A", nitrogen balance was negative; however, when the same subjects ate Diet "B" in which half of the protein was replaced by an equivalent amount of amino acids, nitrogen balances became positive. In the two other subjects presented here, negative nitrogen balances were converted to positive by lowering the amount of fat in the diet by 40–60%.

An example of the worst nitrogen wasting found in this group of patients is presented on this slide. The patient lost 4–7 gm of nitrogen daily on a normal diet; Diet "A". When half the protein in Diet "A" was replaced by equivalent amounts of amino acids, (Diet "B"), nitrogen balances converted from negative to positive. Similarly, when patients ate Diet "A" and received amino acid supplements by a feeding jejunostomy, nitrogen balances became positive.

Three types of dietary manipulations can change nitrogen balances from negative to positive in jejunoileal bypass patients: 1) Lowering dietary fat; 2) Supplying amino acid supplements orally; and 3) Supplying amino acid supplements by feeding jejunostomy.

DR. FRANCIS D. MOORE (Boston): I would like to congratulate Dr. Scott for showing that in this massive obesity, a patient can lose thousands or hundreds of thousands of calories by endogenous fat oxidation without a severe erosion of the body cell mass.

The question is interesting and recalls some work we did several years ago on body composition addressing itself to the problem: Can you lose fat weight without losing cell mass?

In the absence of intake, the answer is *always* negative. The studies of Schrenheimer showed why; that there are some essential carbon skeletons there in muscle protein that the body must have.

But, with exercise and carefully controlled intake, it is possible to lose lots of fat without a serious erosion of the body cell mass.

Dr. Scott has gone ahead and answered an even more interesting question. Very fat people all have abnormal hydration of their body cell mass. Will it go away with fat loss? They seem to have a very high Na:K ratio. I was interested yesterday that Dr. MacLean used that method of expressing abnormal hydration in a different setting. Dr. Scott has shown that with this operation (especially the best of his three procedures) not only does the body cell mass erosion cease but he winds up with a patient who has a much more normal hydration relationship with the rest of his body.

Now, what does that mean? It means that he will be much more effective in terms of muscular exercise. Secondly, he's much less apt to develop arterial hypertension, a serious complication of prolonged obesity and, third, he has less likelihood of developing diabetes.

Dr. Scott has used a whole body counter, which we very much envy. The Mayo Clinic showed, some years ago, that body potassium measured by K-42 dilution or K-43 dilution is essentially the same as that done with the whole body counter.

I'd like to go back to the previous talk for just a moment (Dr. Brennan's) and make two points. One, we're trying to look at a very interesting scientific point that has to do with substrate interrelations and the demonstration that a 3-carbon carbohydrate has remarkable protein interactions with muscle. This is the essence of Dr. Brennan's demonstration.

DR. H. WILLIAM SCOTT, JR. (Closing discussion): Dr. Isaacs, you've certainly made me feel good in that your balance studies tend to support the findings that we had in this study.

I believe you bring out something that's very important and that is that a low fat diet, or fat free diet, can help these individuals adapt and adjust to their new metabolic setup by eliminating obligatory steatorrhea which they will have otherwise with this very small amount of gut available. They're going to have intestinal hurry, but this will reduce it.

They will have inevitably the problem of bile acid malabsorption and this is reflected not only in steatorrhea but in the cation binding and the protein losses that tend to go with this. One of the things we try to get all of the patients to follow is a low fat diet.

They do not do it very well, but if they have it emphasized to them and do tend to follow a low fat diet, we believe this is contributory to their potassium and protein homeostasis.

The points made by Dr. Moore make me want to go and buy another copy of his book, "The Body Cell Mass, Body Composition in Health and Disease." This of course is the "bible" and he is the father of modern body compositional studies. I am really apologetic for using the older term "lean body mass." It should be "body cell mass" as he has pointed out so clearly; even going to the extent of writing a book on this!

Dr. Moore, the large appetite which the obese people have, in our experience, tends to continue and I think this may be supportive of the improved protein nutrition if they eat well and in large volume. Then, the chances are pretty good that their lean tissue support will be intact.

We believe—and we have no proof of this—but we believe that patients after this operative procedure do better if they exercise and push themselves into a program designed to achieve physical fitness. I wish we could get you to tell us, Dr. Moore, whether physical fitness can be related, or in what way can one accurately relate physical fitness to improvement in the body cell mass/body weight ratios which we have achieved in these patients.

We would like to be able to develop an appropriate assessment of this important parameter.

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NEOSPORIN® Powder
(polymyxin B-bacitracin-neomycin)

NEOSPORIN® POWDER
POLYMYXIN B-BACITRACIN-NEOMYCIN
FOR TOPICAL USE ONLY (NOT STERILE)

DESCRIPTION: Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; zinc bacitracin 400 Units; neomycin sulfate (equivalent to 3.5 mg neomycin base) 5 mg; in a special lactose base.

***INDICATIONS:** Based on a review of this drug by the National Academy of Sciences — National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: For topical administration for the treatment of the listed localized infections or for suppressive therapy in such conditions:
Prophylactic: Postoperative and traumatic surface wounds, biopsy sites, skin grafts and donor sites, dermabrasion.
Therapeutic (when infected by susceptible organisms): Vascular ulcers, decubitus ulcers, pyodermas, infected eczemas, infected dermatoses.
Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. It is to be noted that the powder is not intended for sterile use in surgical procedures such as those involving abdominal or thoracic body cavities.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

DOSAGE AND ADMINISTRATION: Apply lightly to the area to be treated as often as needed; treatment area may be covered with a dressing or left exposed, as desired. In biopsy sites, dermabraded areas, etc., the powder may be mixed with a little powdered gelatin foam to provide concurrent hemostasis.

SUPPLIED: Shaker-top vial of 10 g NDC 0081-0744-99.
Complete literature available on request from Professional Services Dept. PML.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

The end of surgery
is only the beginning...

When serious infections* complicate recovery

*due to indicated susceptible organisms

'ANCEF' Reported 90% Effective in Serious Bone and Joint Infections

In clinical studies of 30 patients with such infections as septic arthritis and osteomyelitis due to susceptible strains of *Staphylococcus aureus,* 'Ancef' produced good or excellent† responses in 90% of the cases.

'ANCEF' Penetrates Infected Bone and Synovial Fluid**

Patient	Tissue/Fluid: Biopsy Specimen	Tissue/Fluid Level (mcg/ml) (Sampling time)	Serum Level (mcg/ml) (Sampling time)	Clinical Response†
1	Osteomyelitic Bone	49.4 (1 hour)	30.2 (1 hour)	Good
2	Osteomyelitic Bone	35.6 (5 hours)	26.0 (5 hours)	Excellent
3	Osteomyelitic Bone	22.0 (5 hours)	13.9 (5 hours)	Excellent
4	Synovial Fluid	21 (1 hour) 20 (3 hours) 24 (6 hours)	35 (1 hour) 28 (3 hours) 26 (6 hours)	Good

**(Infections due to susceptible strains of Staph. aureus. Each of the four different patients received 1 gram IM prior to sampling. Therapy was then continued at 1 gram q8h for 13-16 days. Tissue penetration is regarded as essential to therapeutic efficacy but specific antibiotic tissue levels have not been directly correlated with specific therapeutic effects.)

'ANCEF' Offers the Convenience of Both IV and IM Administration

Adverse Reactions

Adverse reactions reported with 'Ancef' include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. Transient rise in SGOT, SGPT, BUN and alkaline phosphate levels has been observed without clinical evidence of renal or hepatic impairment.
For a complete list of adverse reactions with 'Ancef' therapy, please see next page.

Warnings

Cephalosporins should be given cautiously in penicillin-sensitive patients because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.

†Excellent response: Initial improvement at 1-3 days with maximum improvement between 3-7 days.
Good response: Initial improvement at 2-4 days with maximum improvement between 4-10 days.

Please see the next page for a brief summary of the prescribing information.

Smith Kline & French Laboratories, Division of SmithKline Corporation

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

Injection: 250 mg, 500 mg and 1 gram vials

meets the challenge, IV or IM

ANCEF®

brand of
STERILE CEFAZOLIN SODIUM

meets the challenge, IV or IM

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION
Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio] methyl} -8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS
Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).

Streptococcus pneumoniae (formerly *D. pneumoniae)*
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS
Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx, however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS
Ancef (sterile cefazolin sodium, SK&F) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS
Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS
The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible gram-positive cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

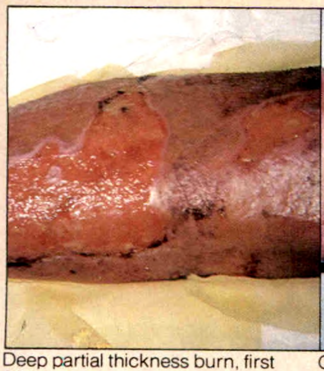
In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

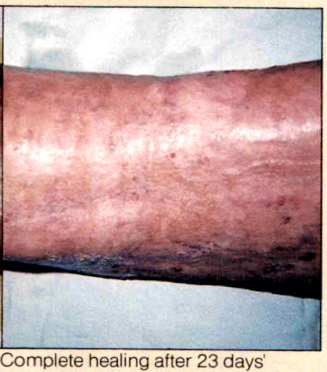
HOW SUPPLIED
Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, PA 19101

Because it's medicated.



Deep partial thickness burn, first 24 hours.



Complete healing after 23 days' treatment with nonadhering XEROFORM Dressings.

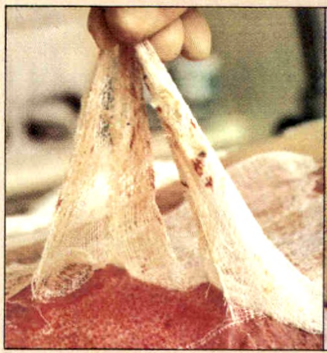
A XEROFORM Petrolatum Gauze Dressing with 3% Bismuth Tribromophenate provides an astringent action that helps maintain a dry wound...and a mild deodorizing action as well.

In addition, published data indicate that XEROFORM Dressings help promote epithelial cell proliferation:

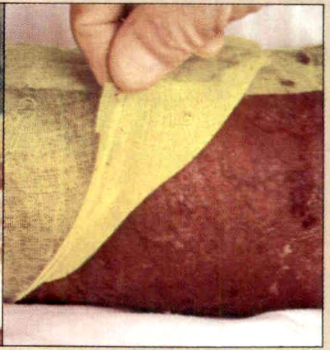
Human study[1] In evaluating the effects of silver nitrate and Sulfamylon® on the epithelization of skin graft donor sites, Bellinger and Conway found that both agents caused delayed healing when compared to the control, XEROFORM. XEROFORM was used as the control because, in their experience, "no environment has been shown to result in faster spread of epithelium...."[1]

Animal Study[2]* Using Sprague-Dawley rats, another group of investigators studied the effect of various topical dressings on donor site epithelization. They concluded: all dressings were superior to the control (exposure to air) and "Scarlet Red and Xeroform were statistically superior to all other dressings [studied] (P< .05)."[2]†

Because it's nonadhering.



Dry gauze dressings that stick to the wound can hurt and can damage new tissue.



Nonadhering XEROFORM Dressings help prevent painful reopening of wound surface—help prevent scarring and infection.

A nonadhering XEROFORM Dressing reduces pain and trauma during dressing change. It clings and conforms to all body contours—yet avoids sticking. So it lifts off easily and comfortably.

While it's on, a XEROFORM Dressing helps protect the wound from environmental contamination; helps prevent unnecessary loss of body fluids.

XEROFORM Dressings are conveniently packaged in peelable foil envelopes, with overwrap available for operating room use. Guaranteed sterile.

Sizes: 1″ x 8″ strips (regular and overwrap), 5″ x 9″ strips (regular and overwrap) and 4″ x 3 yd rolls (regular only).

*Animal data are not intended to imply the same effect in humans. Human studies are now under evaluation.

†Both SCARLET RED and XEROFORM are nonadhering dressings from Chesebrough-Pond's Inc.

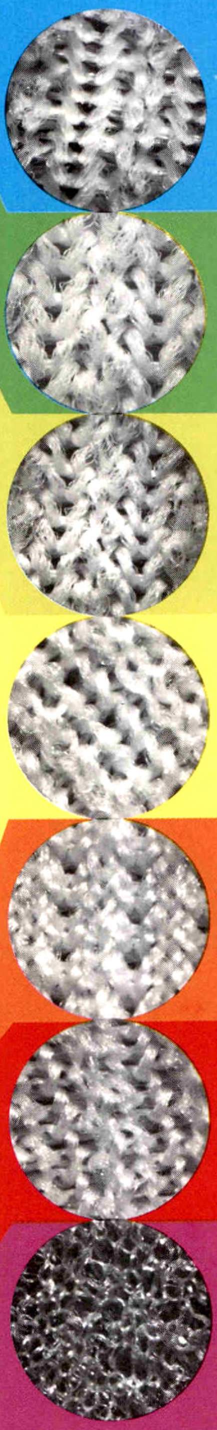
1. Bellinger, C. G. and Conway, H.: Plast. Reconstr. Surg. *45*:582, June 1970.
2. Salomon, J.C., Diegelmann, R.F. and Cohen I.K.: Surg. Forum *25*:516, 1974.

CP
XEROFORM
PETROLATUM DRESSING
NON-ADHERING Fine Mesh Absorbent Gauze (44/36) Impregnated with Xeroform (Bismuth Tribromophenate 3%) in a Petrolatum Blend
Chesebrough-Pond's Inc. HOSPITAL PRODUCTS DIVISION
RE-OR
5-433

XEROFORM. Because it's available.

CP Chesebrough-Pond's Inc.
HOSPITAL PRODUCTS DIVISION
GREENWICH, CONNECTICUT 06830

Because tubular design provides proper graduated compression



The knit is looser at the proximal end of the Zimmer anti-embolism stocking to accommodate the large circumference of the thigh without tourniquet effect. A unique thin foam lining and insert* helps keep the stocking up even when the patient is ambulatory.

The open knit above the knee exerts minimal compression so it will not inhibit blood flow being forced through the venous system by tighter compression distally on the leg.

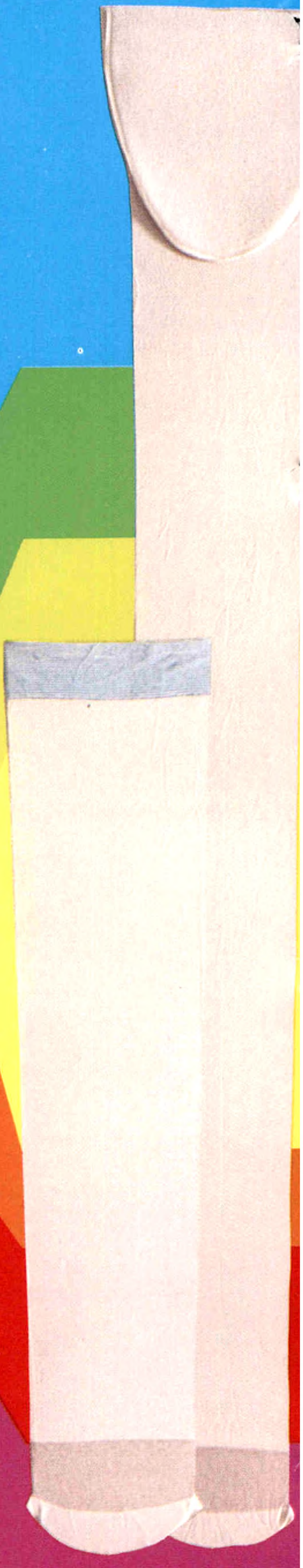
The knit loosens significantly at the knee to minimize pressure on the popliteal vein.

The tight knit over the calf forces the blood into the deep system while it compresses the superficial veins.

The knit is tightest at the ankle to provide the greatest compression distally.

A wide band of lighter knit material facilitates easy application of the stocking and proper fit around the heel and instep.

The transparent toe window allows a quick check of blood circulation without removing or adjusting any portion of the stocking.



* Patents Applied For

the Zimmer anti-embolism stocking

PATENTS APPLIED FOR

Correct graduated compression is now controlled by a single variable — the tightness of the stitch at a given circumference.

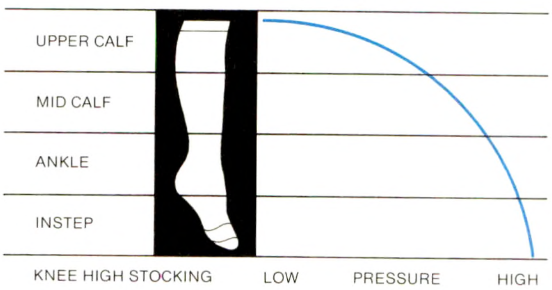
The new tubular design anti-embolism stocking from Zimmer•USA precisely controls compression through the amount of elasticity knitted into the stocking. This unique variable knit* is precisely controlled during manufacture with sophisticated, programmable knitting machines. Because precise control is exercised over the knit at any circumferencial point on the leg, the Zimmer anti-embolism stocking provides gradually decreasing pressure that enhances the venous return mechanism. Tightness of the knit is the key factor controlling the amount of compression.

*Patents Applied For

It shapes itself to fit virtually any leg.

Because no two legs are exactly alike, any pre-shaped anti-embolism stocking may not exactly match the contours of an individual patient's legs. Improper fit could cause constriction at some point on the leg. The stocking's tubular design adapts itself to even slight variations in the contour of a patient's legs and provides correct graduated compression through its built-in graduated elasticity. Available in many size and style combinations — 36 in all — to assure a correct fit for virtually any patient.

GRADUATED COMPRESSION CURVE



CLINICAL REFERENCES available on request from Zimmer•USA

CONTRAINDICATIONS: Do not use in the presence of potentially compromised vascular circulation, i.e., arteriosclerosis, congestive failure, massive edema, etc. Not recommended for use in the presence of open skin lesions or disease. Do not use over the thigh when the thigh circumference is greater than 28".

WARNING: Use proper size of stocking for the patient. Be sure heel is placed in the heel instep band. Discontinue use if circulation is compromised as indicated by pain, loss of capillary pulse in toes, etc. Do not roll down the top of stocking as a tourniquet effect may occur. CAUTION: Federal law restricts this device to sale by or use on the order of a physician.

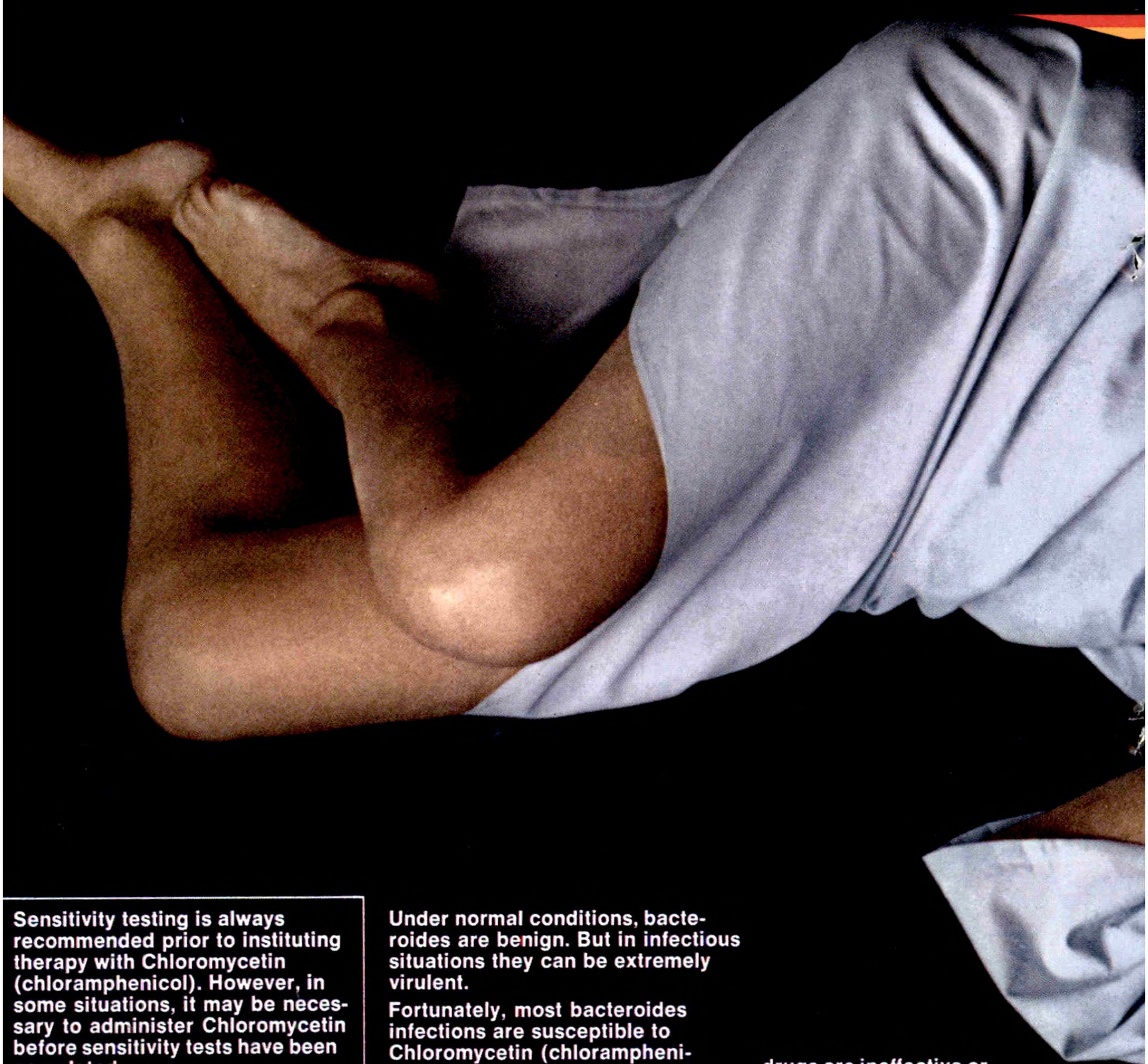
ZIMMER · USA
Warsaw, Indiana 46580

ZIMMER · USA · INTERNATIONAL – Warsaw, Indiana 46580
ZIMMER · CANADA LTD. – Brampton, Ontario / ZIMMER · USA · EUROPA S.A. – Brussels, Belgium
ZIMMER · USA · POULIN – Paris, France / ZIMMER · USA · AUSTRALIA PTY. LTD. – Sydney, Australia
ZIMMER · USA · JAPAN K.K. – Tokyo, Japan / ZIMMER · USA · SURGICAL PRODUCTS LTD. – Auckland, N.Z.

Bacteroides

may be implicated
n a number of clinical situations,
ncluding . . .

- septic abortions
- deep wounds
- bacteremia
- metastatic or other abscesses in association with thromboembolic phenomena



Sensitivity testing is always recommended prior to instituting therapy with Chloromycetin (chloramphenicol). However, in some situations, it may be necessary to administer Chloromycetin before sensitivity tests have been completed.

Bacteroides are the most prevalent microbial flora of man. They are anaerobic, aero-intolerant, nonsporeforming, nonmotile, gram-negative bacilli. They most often appear in mixed infections, and are highly opportunistic. Further, they are very difficult to culture.

Under normal conditions, bacteroides are benign. But in infectious situations they can be extremely virulent.

Fortunately, most bacteroides infections are susceptible to Chloromycetin (chloramphenicol) therapy. Yet, all too often their presence goes undetected. So today, many authorities recommend early—and vigorous—treatment with Chloromycetin when the clinical impression suggests that a *Bacteroides* infection is present.

Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated.

But when bacteroides are implicated, Chloromycetin (chloramphenicol) therapy may well be the conservative course. For, in such situations, the benefits-to-risk ratio with Chloromycetin is very favorable.

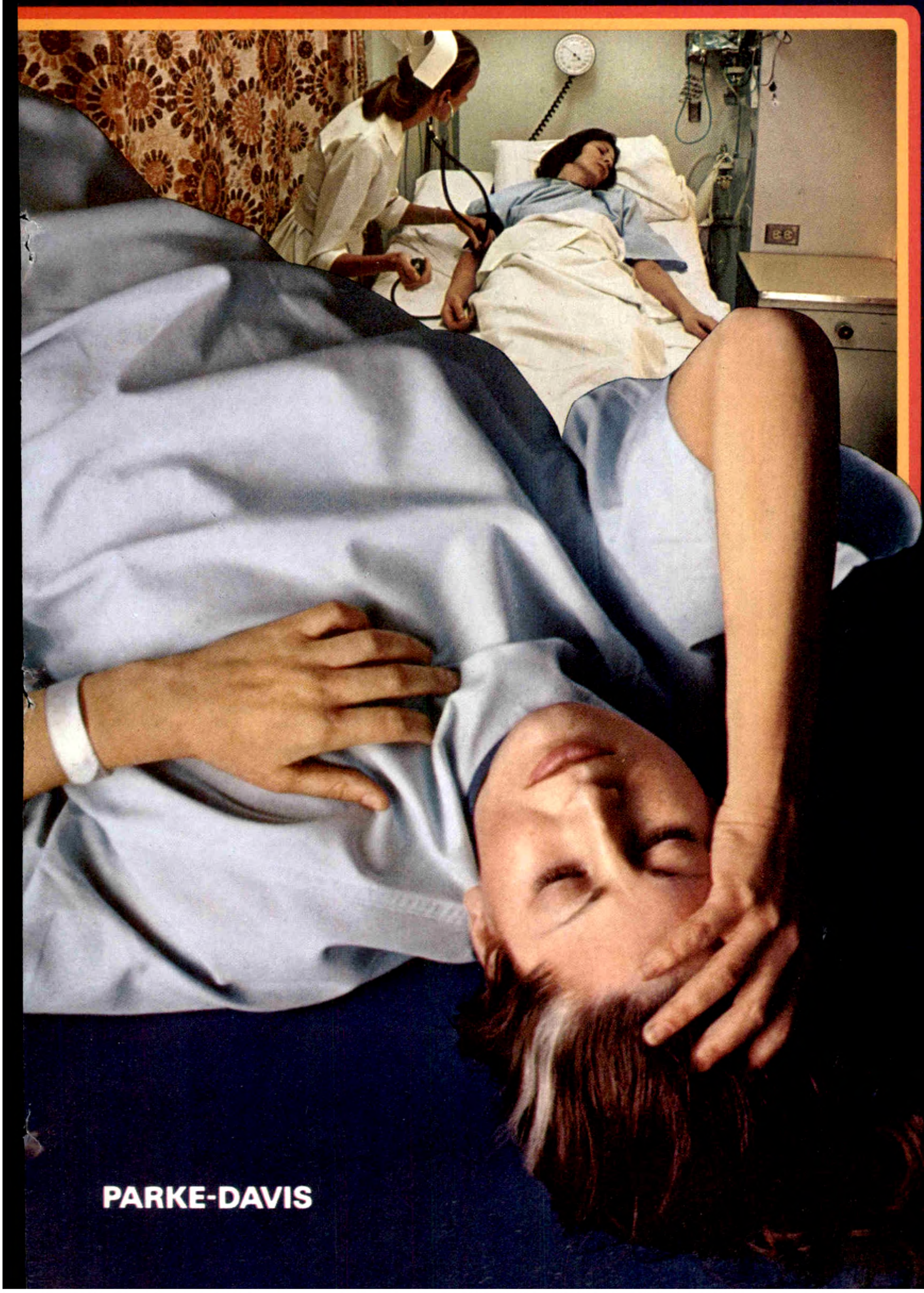
See next page for full prescribing information.

Bacteroides...

often an indication for

CHLOROMYCETIN®

(chloramphenicol) Sodium Succinate



PARKE-DAVIS

Prescribing information—Chloromycetin (chloramphenicol) Sodium Succinate
For intravenous administration

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae.* It is particularly active against *Salmonella typhi* and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**
   It is not recommended for the routine treatment of the typhoid carrier state.
2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.
   a) *Salmonella* species
   b) *H influenzae,* specifically meningeal infections
   c) Rickettsia
   d) Lymphogranuloma-psittacosis group
   e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

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*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.
2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.
4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.
5. There are no studies to establish the safety of this drug in pregnancy.
6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).
7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.
8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
c) The symptoms appeared in the following order:
   (1) abdominal distension with or without emesis;
   (2) progressive pallid cyanosis;
   (3) vasomotor collapse, frequently accompanied by irregular respiration;
   (4) death within a few hours of onset of these symptoms.
d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

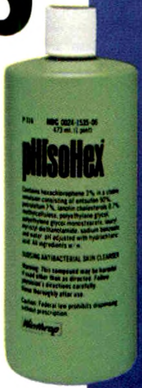
CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off RJ

PD-JA-1280-2-P (2-75)

PARKE, DAVIS & COMPANY, Detroit, Michigan 48232

pHisoHex® between contacts

contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.



Protects every hand... the more it's used

Protects every hospital service... the more hands that use it

Unlike many other antibacterial skin cleansers, pHisoHex® creates a bacteriostatic film that reduces resident hand staph and other gram-positive bacteria to minute fractions of original levels after a few days of regular use. Thus, the pHisoHex hand is continuously protected—even between scrubs—through cumulative action when pHisoHex is used as directed. RINSE THOROUGHLY AFTER USE. pHisoHex should not be used on burned or denuded skin. See brief summary for full details of warnings, contraindications, instructions for use, patient selection, and supply.

Gets between staff and staph

pHisoHex®
sudsing antibacterial soapless skin cleanser
pHisoHex contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control. (See Warnings.)

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

pHisoHex SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene. Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only.* If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly with water.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or gastric lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016

(1653)

DTIC-Dome
(DACARBAZINE)
Sterile

Warning: It is recommended that DTIC-Dome (dacarbazine) be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Since facilities for necessary laboratory studies must be available, hospitalization of patients is recommended. Hemopoietic depression is the most serious toxicity with DTIC-Dome and involves primarily the leukocytes and platelets, although mild anemia may sometimes occur. Leukopenia and thrombocytopenia may be severe enough to cause death.

(See Warnings section.) Studies have demonstrated this agent to have a carcinogenic and teratogenic effect when used in animals.

In treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit against the risk of toxicity.

Description: DTIC-Dome sterile (dacarbazine) is a colorless to an ivory colored solid which is extremely light sensitive.

Action: Although the exact mechanism of action of DTIC-Dome (dacarbazine) is unknown, three hypotheses have been offered:

1) inhibition of DNA synthesis by acting as a purine analog
2) action as an alkylating agent
3) interaction with SH groups

The volume of distribution of DTIC-Dome exceeds total body water content, suggesting localization in some body tissue, probably the liver. It is only slightly (approximately 5%) protein-bound. Its plasma half-life after I.V. administration is approximately 35 minutes. After 6 hours in animal study, approximately 46% of a radio-labeled dose was recovered from the urine. Of this 46%, almost half was unchanged DTIC and a like quantity was AIC (amino imidazole carboxamide) a metabolite. DTIC is subject to renal tubular secretion rather than glomerular filtration.

Indications: DTIC-Dome (dacarbazine) is indicated for the treatment of metastatic malignant melanoma. It has been found that DTIC-Dome (dacarbazine) may be as efficacious at the lower dosage as at the higher dosage. Combinations of cancer chemotherapeutic agents have often shown an improved response over the use of single agents.

Contraindications: DTIC-Dome (dacarbazine) is contraindicated in patients who have demonstrated a hypersensitivity to it in the past.

Warnings: Hemopoietic depression is the most serious toxicity with DTIC-Dome and involves primarily the leukocytes and platelets, although mild anemia may sometimes occur. Leukopenia and thrombocytopenia may be severe enough to cause death. The possible bone marrow depression requires careful monitoring of white blood cells, red blood cells and platelet levels. Hemopoietic toxicity may warrant temporary suspension or cessation of DTIC-Dome therapy.

Precautions: DTIC-Dome (dacarbazine) should be administered preferably to patients who are hospitalized and who can be observed carefully and frequently during and after therapy, with particular reference to the hemopoietic system.

Adverse Reactions: Symptoms of anorexia, nausea, and vomiting are the most frequently noted of all toxic reactions. Over 90% of patients are affected with the initial few doses. The vomiting lasts 1-12 hours and may be completely but unpredictably palliated with phenobarbital and/or prochlorperazine. Rarely intractable nausea and vomiting have necessitated discontinuance of DTIC-Dome (dacarbazine) therapy. Rarely DTIC-Dome (dacarbazine) has caused diarrhea. Some helpful suggestions include restricting the patients oral intake of fluids and food for 4-6 hours prior to treatment. The rapid toleration of these symptoms suggests that a central nervous system mechanism may be involved, and usually these symptoms subside after the first 1 or 2 days.

There are a number of minor toxicities that are infrequently noted. Patients have experienced an influenza-like syndrome of fever to 39°C, myalgias and malaise. These symptoms occur usually after large single doses approximately 7 days after treatment with DTIC-Dome (dacarbazine) and last 7-21 days, and they may occur with successive treatments.

Alopecia has been noted as has facial flushing and facial paresthesia. There have been few reports of significant liver or renal function test abnormalities in man. However, these abnormalities have been observed more frequently in animal studies.

Dosage and Administration: DTIC-Dome (dacarbazine) 100 mg/vial and 200 mg/vial are reconstituted with 9.9 ml and 19.7 ml, respectively, of Sterile Water for Injection, USP. The resulting solution contains 10 mg/ml of dacarbazine having a pH of 3.0 to 4.0.

The recommended dosage is 2 to 4.5 mg/kg/d for 10 days. It has been found that DTIC-Dome (dacarbazine) may be as efficacious at the lower dosage as at the higher dosage. Treatment may be repeated at 4 week intervals. An alternate recommended dosage is 250 mg/square meter of body surface/day I.V. for five days. Treatment may be repeated every 3 weeks. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously.

Injection of DTIC-Dome may be completed in approximately one minute.

Extravasation of the drug subcutaneously during the intravenous administration may result in tissue damage and severe pain.

Any solution remaining in the vial may be stored at 4°C for up to 72 hours. At 20°C, the solution is not stable for more than 8 hours.

Supplied: Vials containing 100 mg or 200 mg of DTIC-Dome as sterile dacarbazine in boxes of 12.

Dome Laboratories

MILES Division Miles Laboratories Inc
West Haven Connecticut 06516 USA

DOM-1260

Dome Laboratories announces

a significant discovery of cancer research

new DTIC-Dome (DACARBAZINE)

a unique agent effective in treating metastatic malignant melanoma

☐ extensively investigated through worldwide cancer research

☐ over 20% remissions documented from evaluation of more than 1400 patients

patients evaluated	complete remission	partial remission	total response	percentage
1427	81	208	289	20.3

☐ a valuable chemotherapeutic agent indicated in the treatment of metastatic malignant melanoma

☐ as with many other cancer chemotherapeutic agents, response to DTIC-Dome may be enhanced when it is combined with other antineoplastic drugs

DTIC-Dome is a new chemotherapeutic agent with a relatively high percentage of reported remissions in the treatment of metastatic melanoma. As with most anticancer drugs, possible beneficial results should be weighed against known risks of toxicity in the treatment of each patient. Toxic reactions are predominantly gastrointestinal and hematologic in nature, requiring that patients be hospitalized during therapy for observation and hematologic monitoring. In general, gastrointestinal symptoms are self-limiting, and reversal of hemopoietic depression usually occurs within three to six weeks after termination of therapy and appropriate corrective measures. (See adjacent page for a more detailed description of side effects.)

Although the exact mechanism of action of DTIC-Dome is unknown, three hypotheses have been proposed: (1) inhibition of DNA synthesis by acting as a purine analog, (2) action as an alkylating agent by release of a mustard radical, and (3) interaction with SH groups.

See adjacent page for full prescribing information.

CEA-ROCHE

Carcinoembryonic Antigen assay

a valuable adjunct during the various phases of cancer management

CEA-ROCHE has been the subject of numerous clinical studies over the past four years to assess its value in cancer management. Most investigators have found this assay to be a useful biological marker for following the clinical course of patients with many types of internal carcinoma.* These studies have reported CEA-ROCHE to be a valuable adjunct in the overall evaluation of the patient's clinical progress and prognosis by indicating...

- lack of response to or escape from therapy
- need for a change or reevaluation of therapy
- development of metastases and/or local recurrence
- the need for more intensive patient examination and observation since a rise in CEA titer has been reported to precede other evidence of recurrence by periods averaging 2 months and up to as much as 29 months.*

CEA-ROCHE may also be used...

- as an adjunct to other diagnostic tests or procedures in the patient suspected of having cancer

*Literature available upon request from Professional Services Department, Roche Laboratories, 340 Kingsland Street, Nutley, N.J. 07110.

ear out here.

CEA-ROCHE
Carcinoembryonic Antigen assay

Suggested Guidelines for the Use of CEA-ROCHE as an Aid in the Management of the Cancer Patient*

Type of Therapy	When to order CEA-ROCHE	Why order CEA-ROCHE
	During Periods of Active Therapy	
Surgery	As part of the presurgical workup and approximately 3 weeks after surgery	To monitor the effects of surgery[1-4]
Radiotherapy	Prior to initiating radiotherapy, once at midpoint and/or upon completion of radiation	To monitor the effects of radiation[1,2,5,6]
Chemotherapy	Prior to initiating chemotherapy, once at midpoint if therapy extends over a 6-week period and upon completion of chemotherapy	To monitor the effects of chemotherapy[1,2,5,7]
	During Short-term Follow-up After Therapy	
All types	Every 1 to 2 months during the first 6 months following therapy	To provide a basis for the reevaluation of therapy and/or an early indication of recurrence or progression of disease[1,2,8]
	During Long-term Follow-up	
All types	Every 6 to 12 months	To provide an early indication of recurrence or progression of disease[1,4,9,10]
	During Active Change in Clinical Condition	
All types	Every two weeks until trend is established	To aid in determining the probable presence of metastases or local recurrence[1,2,4,10]

When using this assay remember CEA-ROCHE is...

- *not* specific for any one type of cancer
- best used *periodically* to establish a trend, usually identifiable within 30 to 90 days
- *not* an absolute test for malignancy and should not be used as the sole criteria for diagnosis (use with other diagnostic tests and procedures)
- *not* recommended as a screen to detect cancer

*These are general guidelines for the use of CEA-ROCHE only and may vary widely depending on such factors as patient status, clinical symptoms, type of malignancy, results of other tests and procedures.

References

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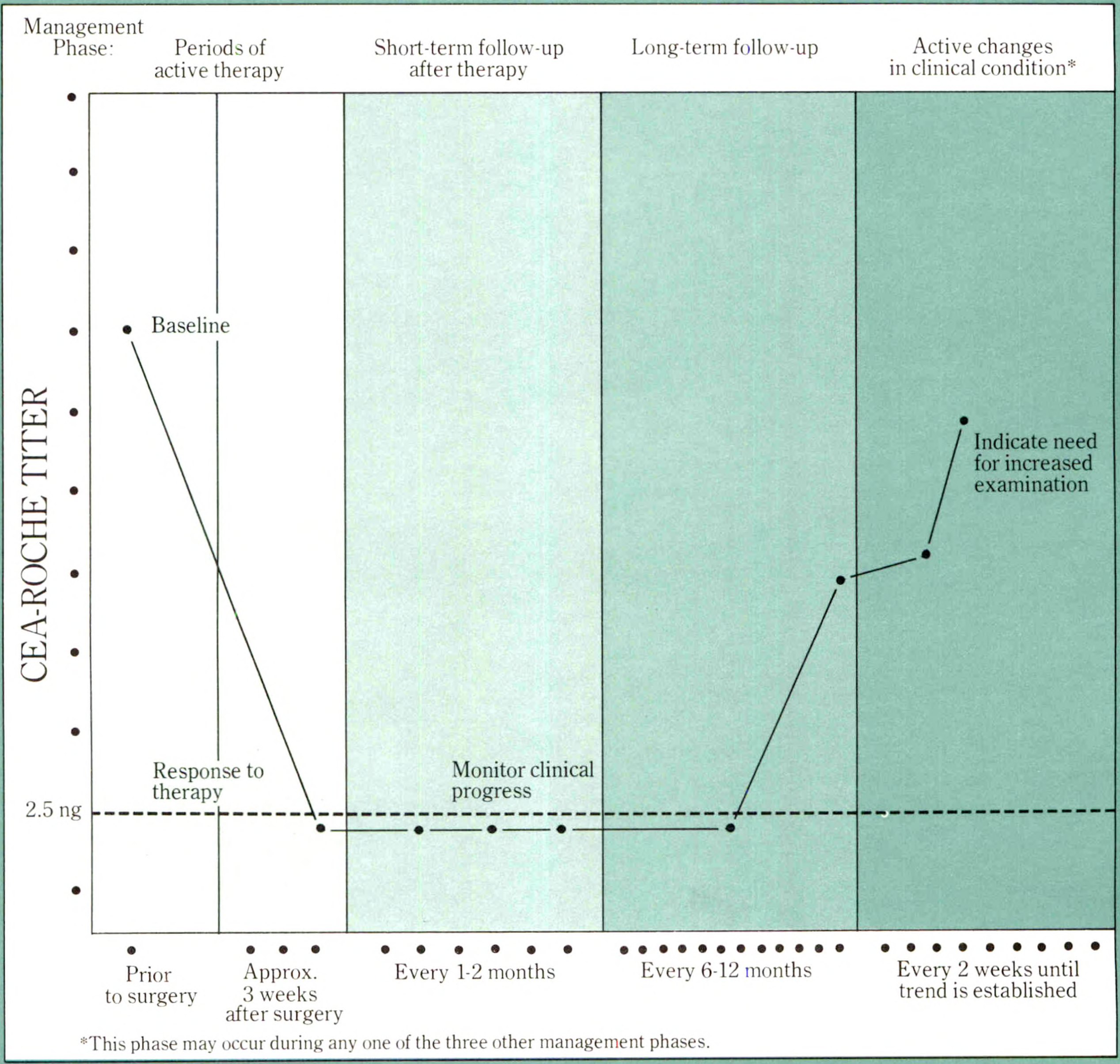
ROCHE

ROCHE

When to use CEA-ROCHE as an aid in the postsurgical management of a cancer patient

A simulation of a representative patient showing graphically when to perform CEA-ROCHE assays using the suggested guidelines appearing on the reverse side.



*This phase may occur during any one of the three other management phases.

CEA-ROCHE may be ordered from
- Roche Clinical Laboratories, Inc., Five Johnson Drive, Raritan, New Jersey 08869 (201) 526-2400
- Major hospital and private laboratories

Additional information may be obtained from
- your Roche Representative
- the Professional Services Department, Roche Laboratories, 340 Kingsland Street, Nutley, New Jersey 07110 (201) 235-4873

Optimizing Results of Gastric Bypass

EDWARD E. MASON, M.D., KENNETH J. PRINTEN, M.D., C. E. HARTFORD, M.D., WILLIAM C. BOYD, M.D.

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Gastric bypass is an extensive gastric exclusion operation used in patients who are more than twice their ideal weight. Most of the early postoperative deaths observed in 3% of 442 patients during the initial 9 years, could have been prevented by more attention to operative technique and early recognition and correction of leaks when they occurred. The best weight loss can be produced by adherence to three components of the operation: 1) Bypass of stomach and duodenum, 2) a small fundic segment and 3) a small (12 mm diameter) gastroenterostomy stoma. The average patient of 142 kg can expect to have a weight of around 107 kg at 1 year and 103 kg at 5 years. Revision of a large stoma to a smaller (9 mm) diameter can induce further weight loss in some patients whose loss has been inadequate. The 1.8% incidence of stoma ulceration may be lowered with the present emphasis on a smaller fundic pouch, but could increase with longer observation. Presently stoma ulcers occur once in every 140 patient years at risk.

GASTRIC BYPASS is a form of surgical intervention designed to limit the intake of food while not interfering with digestion or absorption. It simulates subtotal Billroth II gastric resection with a short loop retrocolic gastroenterostomy, a Hofmeister closure of most of the transected stomach and a 12 mm diameter gastroenterostomy. The excluded stomach can be reanastomosed if needed but in most obese patients the exclusion will be permanent.

Experience with the first 34 patients was reported to this society in 1969.[11] At that time the operation seemed formidable to surgeons who gave it consideration. For example we were using a bilateral supracostal incision extending from the eighth intercostal space on one side to the eighth intercostal space on the other side rather than the short midline upper abdominal incision now in use. The operating time then was 5 hours. The operation had to be simplified if it was to be accepted. We began a series of disappointing attempts to find methods of accomplishing this without compromising effectiveness in weight reduction. The operation now being performed is much like the originally described procedure except that there have been some refinements which have shortened the operating time to 3 hours. We have performed 496 operations on 434 patients.

The senior author has also been disappointed in his belief that collection of a great deal of data and the use of computer analysis[8] could reveal answers to many of the questions which arise in a new and complex clinical study. Indeed, the data has been collected and analyzed, but answers have not been forthcoming. One of the difficulties has been the continual change in operative technique in the effort to simplify the procedure. What will be presented is still more art than science although data collecting and analysis continues.

The justification for use of an operation in any patient is to improve the quality and expected length of life. This

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Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

This study was supported by grant RR59 from the General Clinical Research Center Program of the Division of Research Resources, National Institution of Health.

TABLE 1. *Summary of 9-Year Experience With Gastric Operations For Obesity.*

	Patients	*Operations*
Gastroplasty	57	57
Gastric Bypass	377	377
Gastroplasty to Gastric Bypass		17
Revision of Gastric Bypass		40
Second Revision of Bypass		6
Totals	434	497
Early Postoperative deaths	13 (3%)	*(2.8%)*
Total Deaths	22 (5%)	

implies at least two complex interacting equations identifying 1) the risk of the treatment and 2) the risk of the condition being treated. Each of these is made up of many variables. Hopefully in time and possibly through a cooperative study involving the experience of many surgeons and a large number of patients, these equations can be correctly stated and appropriate coefficients assigned. In the meantime our impression is that this is a worthwhile procedure in selected patients and that we should share some impressions with other surgeons who wish to make use of gastric bypass.

Gastric bypass is a modification of an old operation applied to a new use. The prototype, subtotal gastric resection, provides a rich experience from which many predictions have been made as to the probable effects of gastric bypass. This in turn has encouraged us in a more rapid expansion in the use of gastric bypass than might have been justified if gastric bypass had been a completely new operation.

Results

Table 1 summarizes the overall experience in numbers of patients and operative procedures. The ratio of males to females is 6:16. The youngest patient was 10 years of age and the oldest 68, with a median age of 35. During 1971, 57 patients underwent gastroplasty.[13] Because of their poor weight loss 17 of those patients have had the gastroplasty converted to a gastric bypass. Forty patients have had a revision of their gastric bypass, in order to improve weight loss, and this usually consisted of a reduction in size of the gastroenterostomy stoma. Six patients who still did not have satisfactory weight loss underwent a second revision. There have been 13 early postoperative deaths for a patient mortality of 3% and an operative mortality of 2.6%. There have been additional deaths later, unrelated to the operative procedure, bringing the total number of deaths to 22 or 5% of patients.

Pulmonary embolism occurred in 4 patients on days 1, 1, 7, and 15 following operation. In terms of consecutive patients, these were patients numbered seven, 36, 238, and 385. One additional patient had postoperative thrombophlebitis and early elevation of serum enzymes and serum bilirubin. She seemed to be improving and was discharged from the hospital but 6 weeks after discharge she suddenly became short of breath and died while being brought back to the hospital. At autopsy, aspiration pneumonia was found. There was severe fatty metamorphosis of the liver. There were no other findings to explain her death. Halothane had been the anesthetic agent used during her gastric bypass.

Nine patients died from peritonitis. One of these died on postoperative day 21 from complications related to leakage around a Stamm gastrostomy. Three patients died because of leak where a suture had torn through the wall of the stomach. These sutures had been taken between the anterior wall of the proximal pouch and the posterior wall of the distal pouch to prevent torsion or intussusception of the excluded segment. One patient strained and coughed from the irritation of an endotracheal tube until he eviscerated. He was returned to the operating room and the wound reclosed but peritonitis developed which led to a breakdown of all suture lines including the gastroenterostomy. One patient drank a large volume of water on the first day postoperatively and disrupted her stomach. Three patients had anastomotic leaks which could not be explained and one patient had primary peritonitis.

The incidence of wound problems has continued to run around 8%. Infection is the most frequent of these and the incidence is twice as high as in thin patients undergoing gastric resections.[15] Infection is usually between the skin and fascia and requires open drainage with frequent wet dressings during the hospital stay and then additional weeks of frequent dressing changes at home.

There have been additional late deaths from cardiac disease which was known to be present at the time of gastric bypass. Three patients have died from cancer; one from cancer of the lung at 21 months after gastric bypass, another from carcinoma of the endometrium at 48 months and a third from carcinoma of the larynx at 67 months. A patient with chronic active hepatitis and a large liver at the time of gastric bypass ultimately died of progressive liver disease at 26 months. It did not appear that the course of the liver disease was altered by gastric bypass. Finally, one patient with a lifelong history of syncopal attacks was killed in a one vehicle accident 48 months after gastric bypass.

There have not been any metabolic or nutritional deficiencies that could be assigned to the operation. Several patients have been readmitted and observed and encouraged to eat or even given a short course of gavage feedings to reestablish adequate intake of food and particularly of protein. We now encourage all patients to take multiple vitamin tablets daily for the first few months. Decrease in serum albumin, protracted elevation of liver enzymes, and abnormalities of electrolytes have not been observed.

Stoma ulceration has been diagnosed in 7 patients for an incidence of 1.8%. This calculates to be one ulcer per 140 patient years of exposure. Those patients who develop stomal ulcers almost always have signs and symptoms of blood loss. There may be an occasional patient who has anemia from excessive menses or from a diet of poor composition.

The postoperative bowel habits tend toward constipation rather than diarrhea although the majority of patients have normal bowel habits. The infrequency of diarrhea explains why these patients do not lose protein, water, and electrolytes and why they have consistently normal laboratory data.

Vomiting is an early postoperative complication and may in some patients seem to be of alarming frequency. Its severity has been evaluated with frequent body weights and analyses of serum electrolytes, blood urea nitrogen, creatinine, serum protein, uric acid and liver enzyme analyses. Usually the patients are vomiting only when they overeat or eat too rapidly and all that they lose is the recently eaten food. They do not, therefore, develop hypochloremic alkalosis and their weight loss, urine volume and urine specific gravity data are usually sufficiently near normal that the patients are not readmitted to the hospital. It is possible for obstruction to develop either at the gastroenterostomy stoma or beyond so that the patients do need to be followed, just as any other patient who has undergone a major abdominal operation.

In a search for criteria for selection of patients who would achieve the best weight loss, patients operated upon between May of 1966 and November of 1970 were analyzed.[4] There were 40 patients for whom we had information about weight loss up to 18 months following the operation. Weight loss was used as the dependent variable, and information about sex, age, height, marital status, access to food, frequency of eating, and physical activity were used as independent variables. Preoperative weight, age, sex and height were found to be predictive of weight loss. The other variables did not show any significant relationship. Recently, with a larger number of patients, a longer followup and the use of initial weight, sex, height, age of onset of obesity, present age, and packs per day per years of smoking, as independent variables, additional regression analyses have been done. The only clinically useful preoperative predictors of the weight loss produced by gastric bypass are initial weight and, to a lesser extent, age. The best weight loss occurs in the heaviest patients and in young adults (Figs. 1 and 2). Initial weight and age are not independent. The heaviest patients are usually in the younger age group. Therefore, at least part of the reason that the older patients do not lose as much weight is because they are not as heavy initially. Of course the older patients are also less active and burn fewer calories.

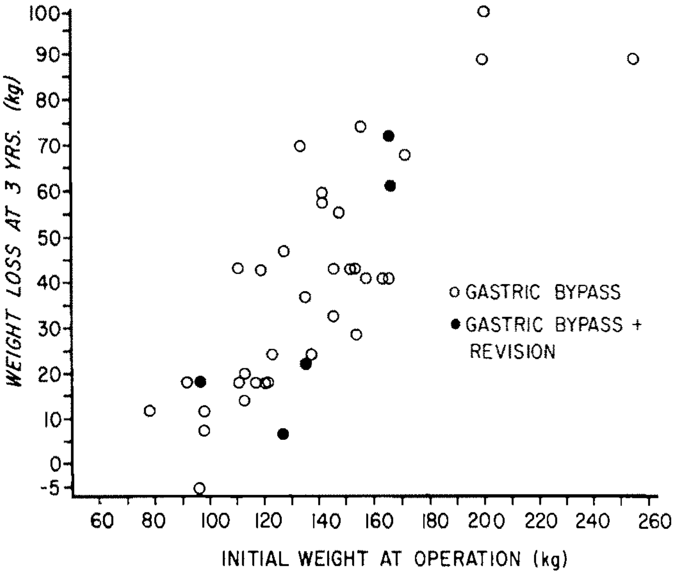

FIG. 1. Weight loss at 3 years following first operation compared to initial body weight, both in kg. The solid dots indicate patients whose initial weight loss was unsatisfactory and who were subjected to a second operation to further narrow the stoma and occasionally to also remove some of the upper gastric pouch. Many of the patients who had the lowest values were over 50 years of age.

The main value of these statistical methods has been in assembling the data in various ways and stimulating our thinking about relationships that might exist. The average weight loss at one, 2, 3 and 5 years remains around 36 kg, nevertheless there are patients who lose a great deal more than this and there are also a few patients who do not lose at all. At three years post gastric bypass the sustained

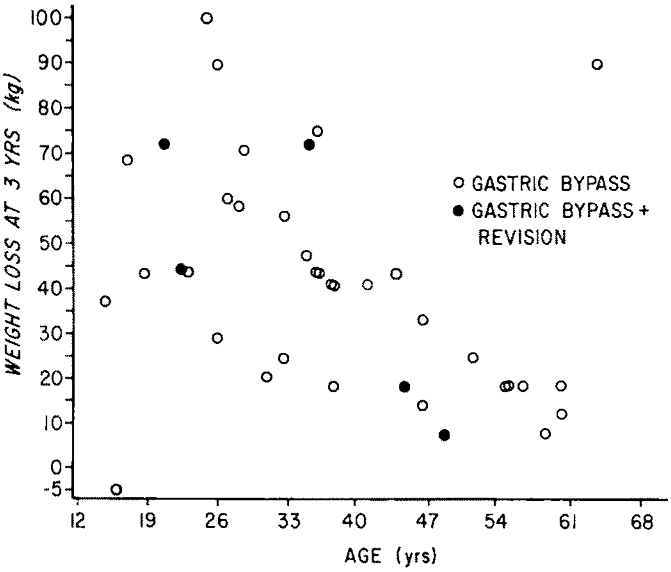

FIG. 2. Relationship at 3 years between weight loss and patient age; solid dots represent patients who underwent revision. Many of the patients who showed poor weight loss because of age over 50 are at the low end of the initial weight scale in Fig. 1.

TABLE 2. *Mean Body Weights By Year of Operation and Elapsed Time.*

		OP	6 WK	6 MO	1 YR	2 YR	3 YR	5 YR
1966-1970	No. cases observed	63	55	59	50	54	34	17
	% cases missing	0	13	6	6	14	46	73
	Mean kg	142	135	116	108	106	101	102
	Minimum kg	80	71	70	56	64	65	67
	Maximum kg	261	250	217	175	182	170	183
1971	No. cases observed	41	37	38	33	28	11	
	% cases missing	0	10	7	20	32	73	
	Mean kg	137	130	120	119	119	122	
	Minimum kg	88	74	66	62	57	53	
	Maximum kg	234	227	209	210	236	179	
1972	No. cases observed	51	46	46	45	37		
	% cases missing	0	10	10	12	28		
	Mean kg	140	136	121	112	108		
	Minimum kg	74	82	76	70	62		
	Maximum kg	215	209	193	174	207		
1973	No. cases observed	132	113	105	104			
	% cases missing	1	15	21	22			
	Mean kg	145	133	120	115			
	Minimum kg	54	48	35	42			
	Maximum kg	250	220	197	191			
1974	No. cases observed	43	30	26	14			
	% cases missing	0	12	40	67			
	Mean kg	144	129	120	108			
	Minimum kg	89	74	82	72			
	Maximum kg	216	190	177	167			

weight loss can be accurately summarized as 50 kg or more in one-third of the patients, between 25 and 50 kg in one-third and less than 25 kg in one-third.

Nine patients with gastroplasty were followed for at least one year after conversion to gastric bypass. They showed a median weight loss of 15 kg before they were converted. The total weight loss was extended to 30 kg one year after conversion. Some gastric bypass patients with unsatisfactory weight loss were revised. Usually this revision consisted of a narrowing of the gastroenterostomy stoma, which can easily be accomplished by exposure of the gastroenterostomy from below the mesocolon. There were 15 who had at least a year of observation after revision. Their median weight loss at the time of the revision was 17 kg and this was extended to a total of 27 kg one year after the revision. The average weights observed over the years are shown in Table 2 with the patients separated into groups by year of the initial operation. The 1966-70 group shows the results that can be obtained with a small reservoir as was being used then. Gastroplasty was used during 1971. In 1972 gastric bypass was resumed but the pouch was not always as small as it had been in 1966 to 1970.

There have been three patients who have had their stomach restored by taking down the gastroenterostomy and reanastomosing the upper segment to the lower segment. One of these was a patient who had multiple complications early after his operation. Another patient who weighed 155 kg had severe pancreatitis. It was elected to go ahead with the gastric bypass to reduce his weight and with the hope that perhaps a reduced food intake and restriction in his ability to drink large volumes of beer might have some beneficial effect on his pancreatitis. It was realized that gastric resection had been tried by others for the treatment of pancreatitis without benefit. However, we thought that, if the pancreatitis persisted, we could probably anastomose a longitudinal opening which would then be made in the pancreatic duct to an opening in the excluded stomach. The pain from pancreatitis did persist but an operative retrograde pancreatogram revealed a normal unobstructed pancreatic duct. Pancreatic biopsy revealed severe atrophy of the exocrine gland, marked fibrosis and nesidioblastosis. A 95% pancreatectomy was performed and the stomach was reanastomosed. This man's weight now is 60 kg. A third patient seemed, by all objective criteria, to have had an excellent result from gastric bypass but returned frequently to her own physician, and to see us, because of bouts of pain and vomiting whenever she tried to work. No explanation could be found for this even at exploration and finally we decided to reanastomose the stomach although it seemed as though her symptoms probably were not related to the gastric bypass. There have been 2 patients in whom excessive weight loss has occurred but in both instances there was no abnormality found in the operative procedure and, as in the case of a few patients with total gastrectomy, a short admission to the hospital for supervised refeeding has solved the problem for both patients. The gastric bypass operation has not required restoration to a normal stomach because of excessive weight loss. We have on occasion had to perform a second operation within 4 to 6 weeks because of a stoma that was too small but the treatment in such situations has been to enlarge the gastroenterostomy by a few millimeters rather than giving up the operation.

Gallstones are much more common in grossly obese patients. Obese patients, even without gallstones, routinely have lithogenic bile with an excessive concentration of cholesterol.[2] In 78 patients the gallbladder was removed during the gastric bypass operation. This adds about 20 minutes to the procedure. Umbilical and preexisting incisional hernias are also common. Repair of these adds about 30 minutes to the operating time (Table 3). We recommend a separate incision for the hernia repair so that the midline upper abdominal incision will not be weakened by any extension of its length. Nevertheless, some incisional hernias occur after gastric bypass. Some hernias are too big to repair until after the patient loses weight (Table 4).

Discussion

Stoma ulcer formation was an initial major concern that led to a number of animal experiments and has received special attention in the observation of these patients. Anemia is a common indication of a stomal ulcer and whenever an unexplained anemia is found the patient should undergo fiberoptic gastroscopy. Some of these patients can be treated medically but usually the appearance of a stomal ulcer calls for a vagotomy and if there is stenosis at the stoma, the stoma needs to be revised. The 1.6% incidence to date is low enough to be acceptable. This is consistent with the observation in pouch dogs that gastric bypass causes a decrease in gastric secretory response to a meal.[10] Recent data, which will be reported at another time, show that the serum gastrin response to a standard milk feeding is reduced following gastric bypass. Unfortunately, we do not as yet have adequate information about serum gastrin levels in patients who have developed stoma ulceration. We have usually removed the excluded stomach to eliminate any source of gastrin in these patients. We have, therefore, treated these patients as though they had severe ulcer disease and we have done everything that we could to obviate a recurrence of ulceration. Renewed emphasis on a very small fundic segment will mean even fewer parietal cells above the stoma and this should further decrease the incidence of stoma ulcer but the hypothesis may require hundreds of patients and years of observation to prove.

TABLE 3. *Median Operating Time and Postoperative Days as Influenced by Addition of Other Operative Procedures.*

	Sample Size	Operating Minutes	Postop Days
Gastric bypass only	250	246.5	9.54
Cholecystectomy added	63	257.0	10.00
Hernia repair added	40	277.5	11.75

TABLE 4. *Operative Procedures Performed Subsequent To and Other Than Gastric Operations.*

	Patients		
	#	Reviewed	%
Incisional hernia, related to gastric bypass	13	331	3.8
Unrelated hernia repairs	15	329	4.4
Removal of skin from arms or thighs	9	335	2.6
Removal of abdominal panniculus	32	312	9.3

Pulmonary embolism has been less common than might be expected with a group of very heavy patients undergoing major abdominal operations. We have encouraged early ambulation and continue to use glucose in all of the intravenous fluids. In a study performed in our hospital, continuous postoperative infusions of 5% glucose, 10% glucose and a combination of 5% glucose and 5% amino acids were all equally effective in the suppression of serum free fatty acid levels.[16] Recently, following the suggestion of Blackburn, et al.[1] we have found that the use of crystalline amino acids without glucose is also effective in maintaining a normal free fatty acid level in the serum. These patients should not be allowed, however, to receive fluids which do not contain either glucose or amino acids since complete starvation, together with the added effects of trauma, can cause dangerously high levels of serum free fatty acids.[6,7,9,14,16] One of the potential hazards of this elevation is intravascular clotting and thromboembolic complications. The incidence of embolism is low enough that we will have difficulty in determining what other measures might be taken to eliminate this problem. A registry of patients from other institutions is probably the only way to obtain the numbers that will be required.

The young woman who died with severe fatty metamorphosis of the liver 6 weeks after gastric bypass and Halothane anesthesia, also poses some unanswered questions. Perhaps if a liver biopsy had been performed at the time of gastric bypass and severe fatty infiltration observed, she could then have been treated with a two week or longer course of crystalline amino acid infusion to reduce the amount of fat in the liver as has been described recently by Heimburger, et al. in patients who developed large and extremely fatty livers after intestinal bypass.[3] Actually, the Halothane anesthesia must be suspect since the liver was not grossly enlarged from fatty metamorphosis at the time of gastric bypass and the serum protein and enzyme levels were normal before operation but became elevated early in the postoperative period. Such a pattern of early liver failure has not been observed in any other patient after gastric bypass.

Cardiorespiratory insufficiency has not been a lethal postoperative problem so far. All patients with obesity so severe as to interfere with breathing and to cause abnormal blood gas levels have been admitted to the hospital and observed under close dietary restriction until they have lost enough weight so that the arterial P_{CO_2} returned to normal. If they have polycythemia, repeated phlebotomies are used until a normal hematocrit persists. When these and other findings such as edema have been corrected, gastric bypass is performed. Such patients may still require assistance from a volume controlled respirator during the early postoperative period. Frequent arterial blood gas measurements are obtained and if, in addition, a patient appears to be tired and breathing inefficiently, an endonasal-endotracheal tube, appropriate sedation and volume assisted ventilation are reinstituted, usually for only an additional one or two days. Most of the patients are extubated in the operating room or in the recovery room but if there is any question about their ability to maintain normal ventilation, the endotracheal tube is left in place and they are allowed to breathe unassisted for a time while blood gases are monitored.

The greatest risk to the patient so far has come from errors in operative technique and delay in recognizing peritoneal soilage during the early postoperative period. Gastric bypass can be a difficult operation. It requires special instruments, experience, better than average surgeons and the kind of expert anesthesiologists and nurses that one finds in a tertiary care center. Every step of the operative procedure requires excellent exposure and this is physically hard work. The procedure has all of the special problems which are known to surgeons acquainted with the performance of a Billroth II subtotal gastric resection with short loop retrocolic gastroenterostomy, a long Hofmeister, and a small gastroenterostomy stoma. In addition, the excluded stomach must remain viable and should be immobilized with several sutures between the Hofmeister closure of the upper pouch and the inverted end of the distal pouch. Sutures approximating the posterior wall of the distal pouch and the anterior wall of the upper pouch are potentially dangerous as they may tear out with distention of either segment. Postoperative distention must be prevented by keeping a nasogastric tube in place until there is evidence from flatus, and from a low residual volume of fluid in the stomach, after temporary clamping of the nasogastric tube, that the gastroenterostomy is open. There have been occasional perforations and leaks because of a combination of edema at the gastroenterostomy stoma and an inability to vomit, plus either an ineffective indwelling gastric tube or too early removal of the tube. A closed segment of this small portion of the stomach is, of course, intolerable and has led to perforation of the fundus. All nurses and physicians who are caring for these patients must be alert for nausea, left shoulder pain, and a feeling of increased fullness and discomfort. If these signs of distention of the small fundic pouch appear, measures must be taken immediately to evacuate the pouch before perforation occurs. The use of a 12 mm diameter carefully constructed stoma, as opposed to an even smaller stoma, should decrease this risk.

The complications that have led to death frequently could have been prevented by more careful attention to the details of the operative procedure. In many instances the death might also have been prevented if there had been: 1) less concern about the supposed predisposition of the grossly obese patient to embolism and cardiorespiratory problems, and 2) more awareness of the tachycardia, tachypnea, fever, elevated white blood count, oliguria and increase in postoperative pain that follows release of digestive juice in the peritoneal cavity. This emergency is easily misdiagnosed as some pulmonary complication in these patients.

A fatality from peritonitis represents at least two and sometimes three errors in patient care. In reverse order of occurrence they are failure of early diagnosis of peritonitis, failure to perform the operation properly in the first place and in some instances, poor selection of a patient. One such patient was over 50 years of age, had severe hypertension and moderately severe rheumatoid arthritis. The sutures cut through her stomach wall, even during the operation. In addition, had she survived it is unlikely that she would have been sufficiently active to have lost the desired amount of weight and because of her age, high blood pressure and other medical problems, her life expectancy was scarcely great enough, even with a satisfactory weight loss, to warrant the risk of this type of treatment.

There is a myth that the stomach has such a rich collateral blood supply that it almost never becomes ischemic. One recent patient had signs of peritoneal insult within 18 hours of gastric bypass. Reexploration at 30 hours revealed that the jejunal loop has been brought up through the mesocolon as intended but the loop had passed between the omentum and greater curvature of the excluded stomach. In addition, a gastrostomy had been placed in the distal segment with a Foley catheter balloon distended and this in turn was obturating and obstructing the pyloric canal. The result of this was the creation of enough pressure against the gastroenterostomy site that the anastomosed area of the stomach had become nonviable and was the site of leakage of gastric juice. Fortunately, early resection of the ischemic area and a new properly placed anastomosis allowed a rapid recovery. Any patient who has had removal of the gastroepiploic vessels during a previous operation is in special need of careful preservation of the lesser curvature blood supply, both above and below the site of transection.

The effectiveness of gastric bypass is dependent upon: 1) the shunting of food around the distal stomach and duodenum, 2) a small gastroenterostomy stoma and 3) a small reservoir between the esophagus and the stoma. None of these objectives can be compromised. In 1971 gastroplasty was used in an erroneous belief that a small reservoir and a small stoma would produce the desired weight loss and that bypass of the distal stomach and duodenum might not be necessary. The weight loss after gastroplasty was inadequate (Table 2) and lasted for only 6 months in many patients. This is similar to the experience of surgeons in comparing Billroth I and Billroth II; the latter patients lost more weight. The improved weight loss which we observed after conversion of gastroplasty to gastric bypass is further confirmation of the importance of bypassing the stomach and duodenum when weight loss is the objective.

Between 1966 and 1971, the gastroenterostomy stomas were made at least 2 or 3 cm in diameter and in fact were not measured. At that time we did not realize that a small stoma was important and we followed the teaching of earlier surgeons that the size of the gastroenterostomy stoma was dependent upon the lumen of the jejunum rather than the diameter of the stoma. This teaching is true only when the stoma is large. Obviously, if there is some virtue in a small stoma then the openings in the stomach and jejunum can be made considerably smaller than the lumen of the jejunum. However, care must be taken not to make them so small that they cause prolonged obstruction.

As with patients treated with gastric resection for duodenal ulcer, about a third of our gastric bypass patients had symptoms of dumping. This added another dimension to the desired results in that the patients were unable to eat rich and high osmotic feedings. Not only did they eat less but they ate food that was better for them. Unfortunately, two-thirds of the obese patients were able to eat and drink high calorie foods without becoming ill. In some of the patients who failed to lose weight, we could see by roentgenograms that there was a marked increase in the size of the jejunum, which assumed the reservoir function of the bypassed stomach. A smaller stoma seemed the obvious answer to this problem. It would delay emptying so that the dumping symptoms would not occur in those who were so predisposed and it would also limit the amount of food that could be ingested at any given time for all patients. Even if only 30% of the patients were potential dumpers, all of the patients could benefit from a small stoma.

This thesis was first tested in the revisions of the stoma in patients who had not had satisfactory weight loss. When the stoma could be reduced to the proper size, the patients did lose weight. In 1972 when we gave up gastroplasty, and began to use gastric bypass a small stoma was again made a part of the procedure. Somewhat later we began calibrating the stoma with Hegar dilators at the time of the operation. During revision of the gastroenterostomy stoma for patients who have unsatisfactory weight loss, it is possible to extend the Hofmeister until the opening is snug around a 9 mm dilator. Because almost the entire circumference of the stoma is already healed from the previous operation, there is minimal edema to contribute to postoperative obstruction. When the stoma is made at the initial operation, the Hegar dilator should be a size 12. Any smaller lumen at the first operation, with the inversion of tissues and postoperative swelling, may lead to temporary obstruction and delay in discharge of the patient from the hospital.

In addition, at the time when gastroplasty was abandoned and we returned to gastric bypass, we began to use a somewhat longer length of greater curvature of the upper pouch in an attempt to make it easier to attach the mesocolon to the stomach above the gastroenterostomy. The vessels were cleared from the lesser curvature near the cardioesophageal junction and the transection was carried out using two or three applications of the GIA stapler. The transection of the stomach was performed in a direction parallel to the greater curvature leaving a tube of stomach along the greater curvature and removing extra tissue from the midportion in an effort to make the upper pouch as small as possible. In the majority of patients, this resulted in a satisfactory weight loss but it was still apparent, in some patients, that an excessively large reservoir had been left (Fig. 3). If too narrow a tube was created along the greater curvature, prolonged obstruction sometimes occurred. Even though emptying was delayed by a small stoma, if the reservoir was too large, it allowed the patients to retain extra food in be-

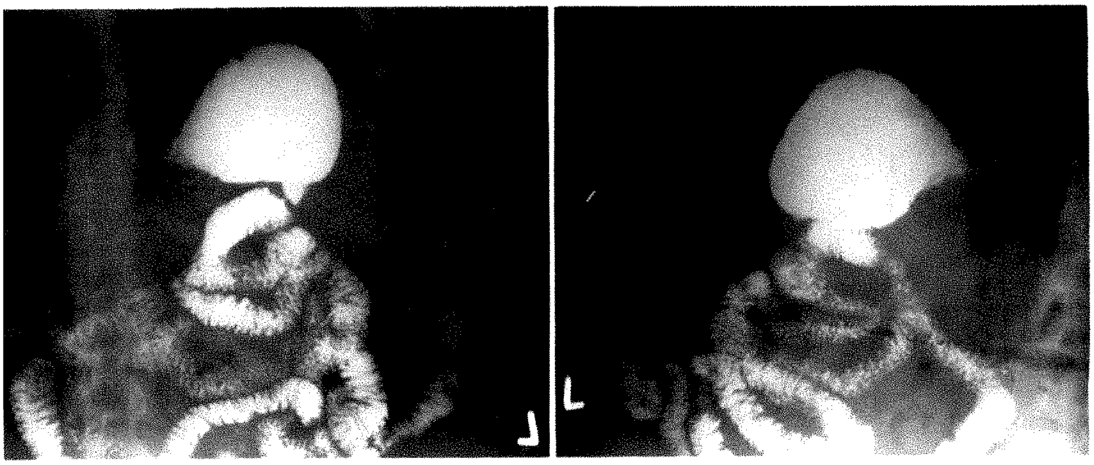

FIG. 3. Anteroposterior (left) and lateral (right) roentgenograms of the operation in which the fundic and upper, vasa brevia attachments are left intact as shown in a Type 1 gastric bypass depicted in Fig. 4.

tween snacks resulting in a continual slow emptying of food into the intestine between meals. a Few patients not only maintained an excessive weight but at the same time complained of foul eructations or periodic vomiting.

These experiences, reinforced by visits with other surgeons who are performing the operation as originally presented, have now led us to the firm conclusion that a small reservoir is just as important as the small stoma and bypass of stomach and duodenum. The small fundic pouch is made by beginning fairly high on the greater curvature, and clearing the vessels and attachments all the way to the esophagus along the greater curvature (Figs. 4 and 5). The upper segment can then be brought down into the wound where it is easily transected, either with several applications of the GIA stapler or by cutting between two parallel applications of the T90. The transection of the greater curvature vessels is greatly facilitated by the use of metal hemostatic clips to secure the vessels rather than attempting to ligate each one. Some ligatures are still required if the clips are pulled off but when this occurs it is usually on the stomach rather than the spleen side and, since the stomach wall is increasingly accessible as the dissection progresses, the bleeding can be easily controlled with suture ligatures.

There are still some patients whose caloric consumption cannot be reduced even by the best of operative procedures. If there were some way to identify these

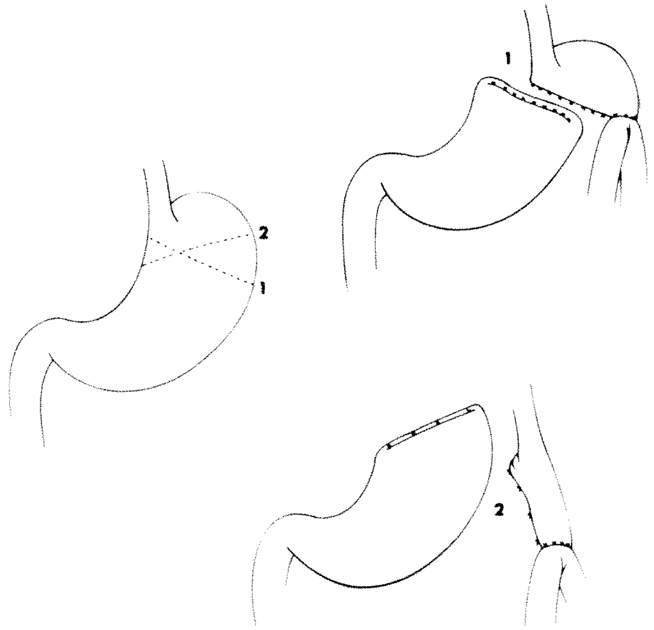

FIG. 4. Two approaches that were used in gastric bypass. In "1" the greater curvature is left long and the transection is carried high on the lesser curvature. In "2" the fundic attachments are cleared. Blood supply is retained high on the lesser curvature. The pouch is smaller but reaches easily below the mesocolon.

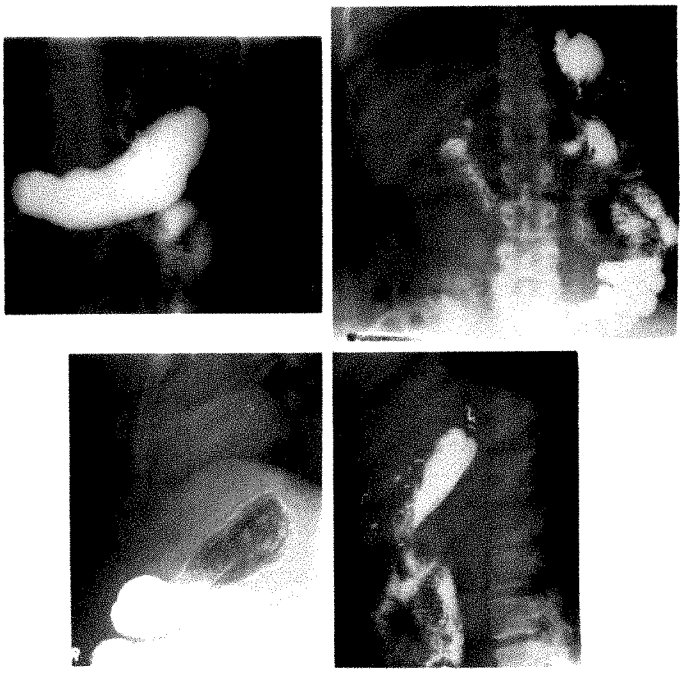

FIG. 5. Shows before (left) and after (right) roentgenograms of a stomach subjected to a type 2 gastric bypass as depicted in Fig. 4. The posterior-anterior views are shown above and the lateral views below. The Type 2 gastric bypass creates a small gastric reservoir which, with a 12 mm diameter stoma, will produce optimum weight reduction.

people they could be spared the operation. At the present time, however, the only objective indices that we have found of use in selecting patients are the initial weight, which should be more than twice the estimated ideal, and an age less than 50 years. Even these criteria sometimes need to be waived. We have the impression that patients who have low intelligence or personality disorders, which make it unlikely that they will be able to work, or play or have interests away from sitting and snacking, are less satisfactory candidates for this type of operation. Perhaps some of those patients who are very firm in their claim that they cannot lose weight on a low calorie diet should also be advised that the operation will not help them, since the only effect of the operation is to reduce intake. The best candidates are young to middle age people who have work and interests which they wish to pursue and who admit that they cannot govern their eating. There are some patients, with multiple physical and emotional problems, who, because of their obesity, will come to the office of any surgeon performing these operations and expect to be made healthy and happy. A few firm selection criteria are of great assistance in refusing to accept patients whose obesity is not their major problem and patients who have unrealistic expectation about solving multiple problems. Most of the late deaths from heart disease and cancer, and one instance of progressive liver disease, could have been excluded from the series by selection of younger less debilitated patients who had more to gain from correction of their excess weight.

For most of our patients the loss of weight and the general feeling of well being is gratifying and often does induce a marked change in life style. Their changes in attitude toward food are often surprising. Most patients remark about their newly acquired disinterest in food. They are pleased that they fill up quickly and that they are not ravenously hungry. This confirms observations of others that obesity is not due to a hunger drive but that the obese patient simply lacks a feeling of satiety. Gastric bypass provides this type of internal sensation so that they know they must quit eating after a reasonable amount of food has been ingested and, furthermore, gastric bypass locates the sensation of fullness where it should be, in the upper abdomen.

Finally, a comparison between surgeons has been made and it was found that those patients operated upon by or under the direct supervision of the senior author have not obtained as great a weight reduction as other patients, except for the earliest group of patients. This is probably due to his continued efforts to simplify the operation. His operative mortality has been only 1.5%, in spite of the fact that he was first assistant in nearly half of the 170 operations in which he was involved. The senior author's acceptance of some poor candidates in an effort to extend the use of this operation account for a majority of the late deaths. These findings suggest that if the operation is used as now recommended, and with proper selection of patients, it can be both safe and effective. The operative mortality should approach 1%, but it can be much higher if others repeat our mistakes, attempt the procedure without adequate preparation and fail to be vigilant in attention to the operative technical details and early postoperative management.

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DISCUSSION

DR. LLOYD M. NYHUS (Chicago): I rise not to speak about obesity, but about the stomal ulcer problem. It is infrequent in discussions to hear the comment "I was wrong!" Following Dr. Mason's presentation on this subject several years ago, I presented a blistering indictment of the concept.

I was concerned that this modification of the antral exclusion procedure of von Eiselsberg would lead to an extensive, indeed unacceptable stomal ulcer rate at the point of a gastrojejuneal anastomosis.

In studies presented elsewhere, Dr. Mason has shown that the residual parietal cell mass bathes the antral mucosa with significant acid to maintain an excellent brake on the gastrin mechanism. Thus, stomal or gastrojejunal ulceration has not been a problem.

I hope in his closing remarks he will give us the exact figures of stomal ulceration in his patients. I know he has had some, but as far as I can tell, stomal ulceration has not been a problem.

Thus, I admit my prediction of catastrophe re the Mason operation for obesity was inappropriate and I now retract my prior condemnation.

Sir Peter Medawar has recently written: "Our advice to those who wish to avoid public penance for making false predictions is not to make predictions at all, unless they are hedged about with the most explicit acknowledgement of the fallibility of all such forecasts." In the future, I shall abide by Sir Peter's rule!

DR. WARD O. GRIFFIN, JR. (Lexington, Kentucky): At the present time we are undertaking a prospective comparison of the two procedures done most often for obesity; namely, jejunoileal bypass and gastric bypass.

I simply would like to second the very careful work that we've heard from Dr. Mason today. At first blush, this would appear to be a difficult operation. It actually, I think, is no more difficult than the jejunoileal bypass, except for the problem of postoperative pulmonary complications which Dr. Mason mentions in his abstract. I wonder if he could fill us in on what he can do, or what we can do, about the pulmonary complications to reduce their incidence.

One other point I'd like to make about this operation is that in the postoperative period, these patients do not require a great deal of medication and therefore it is a very nice operation to use on patients who have less than an adequate IQ.

DR. EDWARD E. MASON (Closing discussion): Dr. Printen uses a temporary gastrostomy in the excluded stomach. I don't really believe that this is necessary, but it has provided an opportunity to collect gastric juice from the excluded stomach and although the volume of gastric juice is considerably reduced, it is not buffered by food and the pH remains low, around 1.9 after a feeding.

Incidentally, studies in dogs have shown that the excluded segment has a very low, or often absent, bacterial content. I think this may be a real advantage of excluding the stomach, rather than removing all of it, because then you don't have the conjugation of bile salts, steatorrhea and problems which occasionally are seen in total gastrectomy.

We have serum post-prandial gastrin analyses before and after gastric bypass, which support our thesis that gastrin secretion is inhibited.

(Slide) We have used a computerized program to derive these curves from the serum gastrin data. The upper curve shows the preoperative and the lower curve the post-gastric bypass gastrin curves.

To answer the question about stomal ulcers, we have observed seven and this calculates out to be one ulcer in 114 patient years of exposure. Now, I think with the stress on the smaller size upper pouch, that this may even be lower. Of course, with more time it could be higher too.

(Slide) I also neglected to mention that we have had studies showing in these patients that they all have lithogenic bile, even if they have not formed gallstones.

We have removed 78 gallbladders containing gallstones in conjunction with gastric bypass, which can be done through the upper abdominal incision with another twenty minutes and it does not add to the postoperative stay. By contrast, some of the people who are doing intestinal bypass, tell me that they have had a significant incidence of acute cholecystitis afterwards because they have hesitated to take out the gallbladder through the incision they were using.

Regarding Dr. Griffin's remarks, I am delighted that a randomized, prospective study comparing gastric and intestinal bypass is under way. Critical evaluation of new procedures by surgeons who have no vested interest is necessary and may save many patients unnecessary risk and morbidity if one procedure is safer and more effective, or if it is discovered that there are certain types of patients who respond better to one operation and other identifiable patients for whom the alternate operation is best. We look forward to the reports of this and other such studies.

Nutritional Consequences of Total Gastrectomy

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Nutritional status was investigated in 10 patients who had previously undergone total gastrectomy without evidence of malignancy. The ability of these patients to ingest and absorb adequate amounts of nutrients was examined. Metabolic balance studies were also performed to discover how effectively these patients could accumulate and use the absorbed nutrients. In the controlled hospital situation, the amount of food ingested was greater than the amount required for maintenance of Ideal Body Weight. Although mild malabsorption of fat and nitrogen was documented, weight gain and positive nitrogen balance occurred. In direct contrast, food intake significantly decreased when the patients returned to their home environment. While severe malabsorption may contribute to malnutrition in the individual patient, the most common mechanism responsible for postoperative malnutrition was inadequate intake. In the occasional patient with severe malabsorption, the universal demonstration of jejunal anaerobic bacterial overgrowth offers important therapeutic implications. The relative importance of pancreatico-biliary insufficiency in promoting malabsorption remains to be determined. Construction of a Hunt-Lawrence jejunal pouch was not found to favorably affect caloric intake, weight gain, degree of malabsorption, or dumping symptoms. Although some degree of malnutrition does result from total gastric resection, in most cases it is mild and potentially correctable. Avoidance of indicated total gastrectomy due to fears of progressive postoperative malnutrition is unwarranted.

ALTHOUGH THE EFFECTS of total gastric resection upon postoperative nutrition have been incompletely studied, incapacitating nutritional debilitation has often been regarded as a necessary consequence of the operative procedure. While significant weight loss after total gastrectomy has been noted by many observers,[1,3,10,20,25,29] both the frequency and the underlying cause of postoperative malnutrition have been controversial. Since previous metabolic studies after total gastrectomy[1,4,6,10,20,22,25,29] have been conducted primarily in patients with gastric malignancy, it has been uncertain whether the development of postoperative malnutrition reflected the progression of malignancy, or resulted from alterations in the physiology of digestion and absorption induced by the surgical procedure per se. A few workers[3,24] have felt that malabsorption was responsible for postoperative malnutrition, while others have suggested that the major cause of malnutrition was inadequate caloric intake.[2,6,20,31] Based upon the latter premise, several authors[17,21,25,29] have advocated the construction of substitute gastric pouches in order to increase postoperative food intake. However, since little comparative data have been available to support these recommendations, the nutritional value of pouch reconstruction has not been established.

The present study was concerned with investigating the cause of postresectional malnutrition and whether the construction of an enteric reservoir offered any demonstrable nutritional advantage.

Patient Population

Since 1966, 42 patients have undergone total gastrectomy at Emory University School of Medicine and Affiliated Hospitals. In 19 of these cases, neither anatomic nor histologic evidence of malignancy was found. Surgical indications in these 19 patients included: 13 patients

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TABLE 1. *Identification Data on Total Gastrectomy Patients*

Patient	Age, Sex	Diagnosis	Reconstructive Procedure	Interval Surgery to Study (months)	Present Occupation
MH	53, M	ZE Syndrome	Hunt-Lawrence; Roux-en-y	68	Unemployed
AR	64, M	Gastric Ulcer	Esophagojejunostomy; Roux-en-y	66	Retired
JL	40, M	ZE Syndrome	Hunt-Lawrence; Roux-en-y	51	Auto Mechanic
WM	74, M	Recurrent Duodenal Ulcer	Hunt-Lawrence; Roux-en-y	94	Retired
WO	45, M	Gastric Ulcer	Esophagojejunostomy; Roux-en-y	17	Painter
CB	31, M	ZE Syndrome	Hunt-Lawrence; Roux-en-y	3	Computer Technician
BQ	36, F	ZE Syndrome	Hunt-Lawrence; Roux-en-y	3	Housewife
TJ	39, M	ZE Syndrome	Esophagojejunostomy; Enteroenterostomy	5	Unemployed; expired with extensive pneumonia one year after surgery
TS	44, F	ZE Syndrome	Hunt-Lawrence; Roux-en-y	6	Housewife
ET	55, F	Gastric Ulcer	Hunt-Lawrence; Roux-en-y	4	Housewife

with markedly elevated serum gastrin levels (>500 pg/ml) and basal hyperchlorhydria (>10 meq/hr) with a presumptive diagnosis of Zollinger-Ellison syndrome, in whom neither the primary tumor nor any metastases could be demonstrated at surgery; 3 patients with gigantic benign gastric ulcers; 2 patients with chronically recurring marginal ulcers with normal serum gastrin levels; and 1 patient with persistent hemorrhage from stress ulceration.

Significant surgical complications developed in only 2 of these 19 patients. Partially disrupted anastomoses occurred in both cases, ending fatally in one patient. Ten patients gave their informed consent to participate in this metabolic balance study. Of the remaining 9 patients who were not included in this report, 6 refused an invitation to participate in the study claiming satisfaction with the results of surgery, one alcoholic patient was lost to followup, one patient died from surgical complications, and one patient could not tolerate the balance diet.

Personal data on the 10 participating patients are summarized in Table 1. The group seemed reasonably homogeneous: 6 patients had ZE syndrome, 4 patients had complicated duodenal or gastric ulcers; 6 patients were over 50 years of age, 4 were under 50 years; there were 7 males and 3 females; 5 patients were studied within the first postoperative year, 5 after this period; 7 had pouch reconstruction and three did not. Following recovery from surgery, 6 of these 10 patients were able to return to their preoperative occupations, 2 continued retired, and 2 remained unemployed.

Methods of Study

Each consenting patient was admitted to the Emory Clinical Research Facility for a minimum protocol period of 18 days. All serum specimens with the exception of those required for determination of carbohydrate absorption by D-xylose and glucose tolerance tests were drawn on the day of admission. For the next 3 days the patient was permitted an ad-libitum "smorgasbord" diet while an accurate record was kept of total caloric intake and the proportional amounts of protein, fat, and carbohydrate selected by the patient. Under the conditions of this diet the only limiting factors in determining the amount or type of oral intake were the patient's desires.

On the morning of the fourth day, per oral jejunal intubation was accomplished via fluoroscopic guidance. Jejunal aspiration and biopsy were done using the Carey capsule in a Quinton multipurpose carrier with an attached sterile polyvinyl tube. Biopsy specimens were placed in formalin for light microscopy. In 3 cases an extra biopsy specimen was taken and placed in 2% D-glutaraldehyde for study by the scanning electron microscope. Jejunal aspirate was collected under sterile and anaerobic conditions. One portion was placed in ice for subsequent determination of bile salts by thin layer chromatography after the method of Gregg.[15] The remainder of the aspirate was immediately placed in a "glove-box" anaerobic chamber. Serial dilutions of aspirate in brain heart infusion (BHI) broth from 10^1 to 10^{10} were used for plating. After 48 hours of incubation, BHI subcultures of individual morphologic species were done, followed by 5 more days of incubation. The BHI subcultures were then streaked on blood agar to distinguish between microaerophilic, facultative, strictly anaerobic, or aerotolerant anaerobe. Anaerobic organisms were further classified by their gas chromatographic patterns of glucose metabolism and other biochemical reactions to various complex sugars, as outlined in the Virginia Polytechnic Anaerobe Manual.

Following the 3-day smorgasbord period, all patients were then equilibrated for 3 more days on an 80 gm protein, 100 gm fat diet. The metabolic balance period consisted of the following 6 days which were divided into two consecutive 3-day periods for stool collection and daily 24 hour urine collections. Specimens were analyzed for fat, nitrogen, Na, K, Cl, P, Ca, and Mg. Three patients had an additional collection period when dietary fat intake was reduced to 50 gm/day. The reported absorption data are, therefore, an average of at least two collection periods in all patients. In separate admissions, one patient with steatorrhea previously documented by these methods was equilibrated on a 100 gm fat diet and then given pancreatic enzyme replacement.* Another patient with previously documented steatorrhea was equilibrated on a 100 gm fat diet which was composed of pre-digested fat.†

During the last three days, the part II Schilling test of vitamin B_{12} absorption was carried out, barium small intestinal transit time was measured, and D-xylose absorption and glucose tolerance tests were done.

Fecal and urinary specimen analyses for nitrogen were done by the micro Kjeldahl method.[16] Stool fat was determined by the method of van de Kamer.[32] The various elements were determined by flame or atomic spectrophotometry. Daily elemental balances for the 6 day period were calculated by subtracting both the creatinine corrected urinary output and the daily fecal output from the daily oral intake of each specific element. Patient education regarding the keeping of a dietary history began with conferences with our Chief Dietician who stressed both the necessity and the technique for accurate measuring and recording of all food intake. Upon leaving the hospital the patient was given the Nutran Daily Food Diary to keep for 7 days. Daily telephone calls by the dietician assisted accurate compliance. Dietary history information was analyzed by a specially developed computer program. Statistical analyses were carried out using Student's "t" test and a two-tailed criterion of significance. All calculations were rounded off to the nearest value in the next decile.

Results

Clinical Data

History. Pertinent historical responses are summarized in Table 2. Four patients had resumed their standard pattern of 3 daily meals. Only 3 patients, two of whom had been recently discharged, continued the 6 feeding schedule recommended at the time of discharge. The time taken to consume each individual meal was surprisingly short, averaging 15 minutes. Nine of the 10 patients experienced early satiety regardless of the method of reconstruction. However, the patients without pouches reached satiety more rapidly than those patients with pouches.

Three patients experienced dumping symptoms, requiring post-cibal recumbency in only one patient. Two patients experienced post-cibal diarrhea with excess carbohydrate intake without other stigmata of dumping. Neither dysphagia nor emesis was a prominent complaint. Two patients with Hunt-Lawrence reconstruction complained of occasional mild sub-sternal pyrosis. One patient with an esophagojejunostomy and Roux-en-y suffers from more severe symptoms of esophagitis which are controlled with an elevated sleeping position and avoidance of spicy foods. Several patients felt that eructations and flatus had become more prominent as a result of the operative procedure. None of the patients experienced any persistent social embarrassment however. Four patients noted occasional mild to moderate abdominal pain usually related to meals. A feeling of weakness with exertion was noted by 6 patients but was physically restricting in only one. None of the patients experienced more than two stools per day in spite of the fact that only one of the 10 patients thought that her stool was normal. The nine other patients complained of poorly formed, foul-smelling, or floating stools.

There were no significant differences in any of the historical responses between sub-groups of these patients comprised of those with and without pouch reconstruction, those studied before or after the first postoperative year, or those with or without Zollinger-Ellison syndrome ($P>0.05$ in each case).

Body Weight. Comparative body weight patterns are shown in Table 3. At the time of this study these patients weighed an average of 15% less than their Ideal Body Weight (IBW).* However, since individual body weights prior to illness had exceeded Ideal Body Weight in all cases, the actual weight loss was much greater, averaging 25 kg. The majority of the weight loss in these patients occurred *prior* to surgery, averaging 20 kg, but another 8 kg was lost in the peri-operative period. The average weight gain after surgery was only 3 kg. Although none of these patients were able to return to their pre-illness weight, 5 patients were able to achieve 90% or more of IBW. Four patients exhibited weights less than 75% of IBW and appeared quite thin.

With one exception, there were no significant differences in any weight parameter between sub-groups made up of those with and without pouch reconstruction, those studied before or after the first postoperative year, or those with or without the Zollinger-Ellison syndrome ($P>0.10$ in all cases). The single exception existed as a difference in Ideal Body Weight between patients studied before and those studied after the first postoperative year ($P<0.01$). This was not surprising since the lesser Ideal Body Weight group contained all 3 females.

Smorgasbord. The intake of specific food constituents during the three day smorgasbord diet period is shown in Fig. 1. Although rather wide variation between individuals is apparent, it is clear that these hospitalized patients were able to exceed the various Recommended Dietary

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*Viokase®-two tablets before, during, and after each meal

†Viokase®-treated corn oil (56% free fatty acids)

*Optimum weight for height, sex, and age: Metropolitan Life Insurance Company.

TABLE 2. *Pertinent Historical Data*

Patient	Number of Meals Daily	Average Eating Time	Early Satiety	Dumping Symptoms	Dysphagia	Vomiting	Pyrosis	Eructations	Flatus	Abdominal Pain	Weakness with Exercise	Number of Stools/Day	Character of Stools
MH	4	22"	2+	1+	—	—	1+	→	→	1+	2+	1	Poorly formed; foul smelling; related to meals
AR	3	10"	1+	—	—	—	—	↓	→	—	—	2	Foul smelling; float on surface
JL	3	15"	2+	3+	—	—	1+	→	→	—	1+	1	Foul smelling
WM	6	10"	2+	—	—	—	—	↓	→	2+	2+	1	Poorly formed
WO	3	7"	3+	—	—	—	3+	↑	→	2+	—	2	Foul smelling; float on surface
CB	6	12"	2+	1+	—	—	—	↑	↑	—	—	2	Float on surface
BQ	3	20"	1+	—	—	—	—	↑	↑	—	1+	1	Normal
TJ	5	15"	2+	—	—	—	—	↓	↑	—	2+	2	Foul smelling; float on surface
TS	6	15"	3+	—	—	2+	—	↑	→	1+	—	2	Related to meals
ET	5	15"	—	—	2+	—	—	↑	↑	—	3+	2	Foul smelling; float on surface

+ = Present
— = Absent
↑ = Increased
↓ = Decreased
→ = No Change
1+ = Mild
2+ = Moderate
3+ = Severe

TABLE 3. *Comparative Body Weight Patterns*

Patient	Height (inches)	IBW* (kg)	Pre-illness Weight (kg)	Pre-op Weight (kg)	Immediate Postop Weight (kg)	Weight at Time of Study (kg)	% IBW at Time of Study
MH	68¼	65	73	53	48	46	65
AR	69	71	77	75	68	70	98
JL	68½	70	80	66	59	65	93
WM	71	75	81	52	41	52	70
WO	67½	68	69	61	49	51	75
CB	62¼	59	82	63	49	55	95
BQ	65¼	59	113	48	43	64	110
TJ	66¼	65	97	57	53	46	70
TS	65½	60	61	59	57	56	93
ET	64¾	58	73	68	55	50	86
Mean	—	65.0	80.5	60.2	52.2	55.5	85.5
Standard Error	—	1.9	4.7	2.6	2.5	2.6	4.7

*Ideal Body Weight chart from Metropolitan Life Insurance Company

Allowances* (RDA) for all the substances evaluated except sodium, magnesium, fluoride, and folic acid. Of particular interest is the observation that 9 of 10 patients approached or exceeded the RDA for calories, 8 of 10 for carbohydrate, 9 of 10 for fat, and 10 of 10 for protein. Insignificant differences of the specific constituents were found to exist between sub-groups of these patients comprised of patients with and without pouch reconstruction, with and without Zollinger-Ellison syndrome, and whether studied before or after the first postoperative year ($P>0.05$ in each case).

Dietary Histories. After returning to the home environment the average daily caloric intake was only 85% of the RDA required for the maintenance of Ideal Body Weight (Table 4 and Fig. 2). The average caloric intake was less than the recommended level by 348 Kcal/day. The largest decrease was noted to be in the carbohydrate fraction, patients ingesting only 63% of the RDA. Fat intake remained essentially the same as the intake during the controlled hospital period, while an increase in protein intake was noted. When the average daily intake in the individual home environment is contrasted to the

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*National Academy of Science, Food and Nutrition Board (corrected for sex and age).

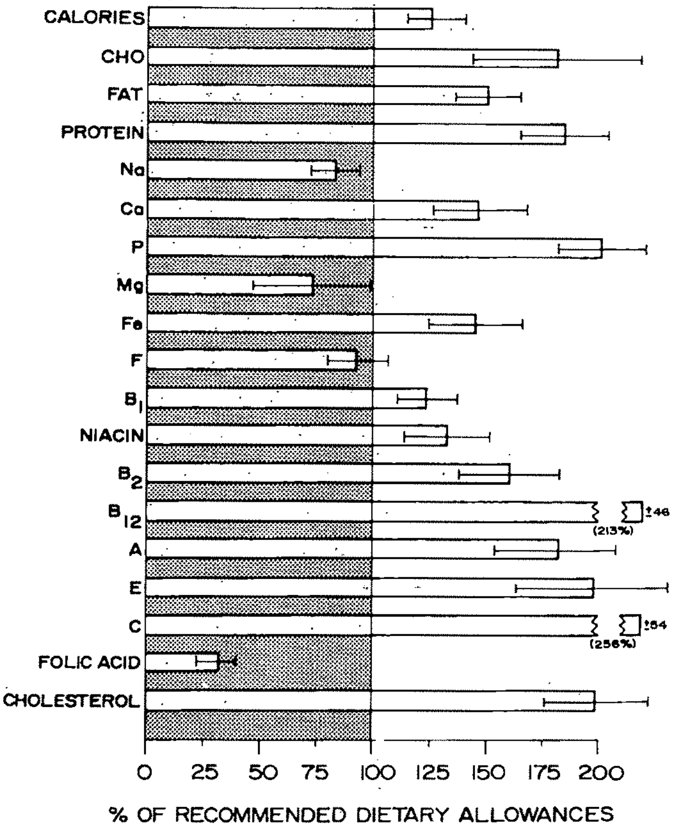

FIG. 1. Voluntary intake of various nutrients during the 3 day smorgasbord period expressed as a percentage of Recommended Dietary Allowances. Results are average values ± the standard error.

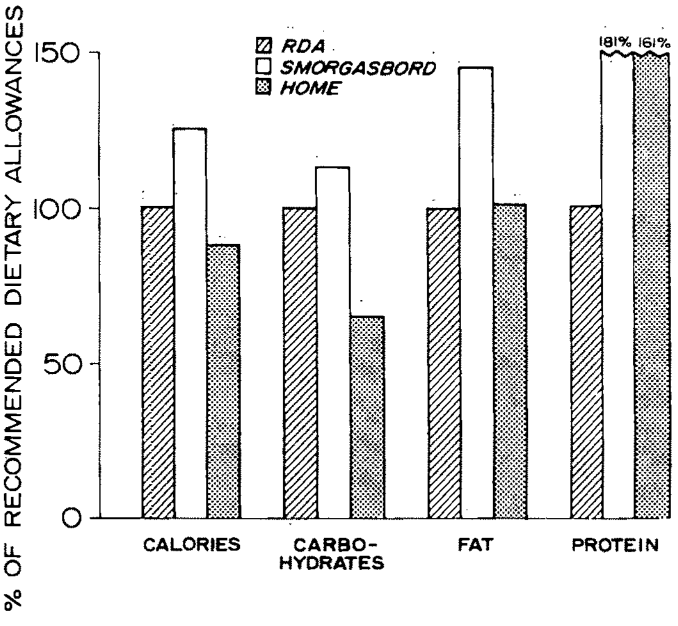

FIG. 2. Voluntary food intake as a function of environmental situation. Note decline in caloric intake in the home environment.

TABLE 4. *Voluntary Food Intake in Individual Home Environments Compared to RDA and Hospital Smorgasbord Intake*

Patient	Calories (Kcal)			Carbohydrate (gm)			Fat (gm)			Protein (gm)		
	RDA	Hosp	Home	RDA	Hosp	Home	RDA	Hosp	Home	RDA	Hosp	Home
MH	2406	2334	1627	333	263	171	94	103	67	56	89	67
AR	2355	3650	3762	295	404	353	103	178	154	59	121	138
JL	2700	3510	3396	383	368	238	105	182	181	56	115	174
WM	2388	2269	1883	333	230	180	93	123	85	56	67	99
WO	2605	3725	1254	320	460	168	100	160	47	65	116	44
CB	2818	1860	1183	260	254	104	100	67	55	65	61	49
BQ	1947	2862	1955	279	457	224	78	86	82	46	77	81
TS	1995	3053	1340	279	293	134	77	161	66	48	119	60
Mean	2402	2908	2050	310	341	197	94	133	92	56	96	89
Standard Error	110	248	350	14	33	27	4	16	17	2	9	16
% of RDA	100	121	85	100	110	63	100	141	97	100	171	158

average daily intake during the hospital smorgasbord period, the results become even more striking. After leaving the hospital caloric intake declined 29% from the values established during the smorgasbord period. Carbohydrate, fat, and protein intakes declined 42%, 30%, and 7% respectively.

Essential Elements

Absorption Studies. The data regarding absorption from the balance diet are shown in Table 5.

Alterations in carbohydrate absorption during a three hour glucose tolerance test were reflected by early hyperglycemia (>200 mg% at 30 minutes) in 8 patients, followed by delayed hypoglycemia (<70 mg% at two or three hours) in 8 subjects. Abnormally low absorption of D-xylose as reflected by low urinary values (<4.5 gms/5 hrs) was observed in 4 patients.

The average value for fecal nitrogen was 2.3±0.3 gms. Azotorrhea (stool N>2.0 gms/24 hrs) was noted in 5 of the 10 patients and accounted for an increased coefficient of nitrogen malabsorption (18.1%±2.7%). All patients with normal serum albumin levels showed normal nitrogen absorption, while 2 of the 5 subjects with nitrogen wasting exhibited low serum albumin levels.

Fecal fat excretion averaged 17.1%±4.6% of ingested fat. Six of 10 patients experienced steatorrhea as defined by a stool content of 10 gms of fat or more on a 100 gm intake. When the fat intake was reduced to 50 gms in three additional studies, the coefficient of fat malabsorption was relatively unchanged (14%±8.1%). Each of the 6 patients with documented steatorrhea had abnormally low values of serum carotene (<50 mg%). Two patients exhibited values for serum cholesterol less than 150 mg%, both of whom had steatorrhea. Five of the 6 patients with steatorrhea also had azotorrhea. Abnormalities in D-xylose absorption, serum albumin, serum carotene, and serum cholesterol only occurred in those patients with malabsorption of fat or protein.

By using the average coefficients of malabsorption for nitrogen and fat, the daily caloric loss due to malabsorbed fat and protein can be calculated. On an 80 gm protein—100 gm fat diet, an average of 84 Kcal/day will be lost (3 gm protein x 4 Kcal/gm+8 gm fat x 9 Kcal/gm). However, on occasion caloric loss due to malabsorption in individual patients was striking. The most marked caloric loss of fat and protein occurred in patient TJ, representing 530 Kcal/day.

There were no significant differences in carbohydrate, nitrogen, or fat absorption between any of the previously mentioned sub-groups (P>0.05 in all cases).

Direct studies of vitamin absorption were not carried out as such. No clinical deficiencies of water soluble vitamins were appreciated. Indirect evidence of adequate levels of vitamins D and K were normal values for serum calcium, alkaline phosphatase, and prothrombin time in each patient. Repeatedly normal serum determinations of Na, K, Cl, and Mg were noted.

Balance Studies. The average daily increments in the total body balance of N, P, Ca, Mg, Na, K, and Cl are listed in Table 6. Each of these individual elements was found to be in positive average daily balance during this controlled period. Taken collectively, these data document the capability of these patients to maintain positive balances of nitrogen and these essential minerals, a requisite condition for weight gain.

There were no significant differences between any of the individual components of the balance studies with regard to sub-groups composed of patients studied before and after the first postoperative year, those with or without Zollinger-Ellison syndrome, or those with or without pouch reconstruction (P>0.10 in all cases).

Additional Studies

Jejunal Cultures, Biopsy, and Bile Salt Analysis. In contrast to the normal subject with an intact stomach where total bacterial counts in the jejunum are less than 10^3/cc and anaerobes are rarely found, the number of

TABLE 5. *Absorption Studies on Balance Diet*

	Carbohydrate						Nitrogen				Fat				
Patient	Glucose Tolerance 0	30	1	2	3	D-xylose (>4.5 gm/5 hr)	Daily Intake (gm)	Daily Stool Output (gm) (<2.0)	Coefficient of Malabsorption (<15%)	Serum Albumin	Daily Intake (gm)	Daily Stool Output (gm)	Coefficient of Malabsorption (<10%)	Serum Carotene 50-300 mg%	Serum Cholesterol 150-250 mg%
MH	90	258	336	354	84	4.0	12	3.0	25%	3.3	100	24	24%	5	115
AR	86	234	158	50	76	3.0	13	3.5	27%	3.9	100	24	24%	38	170
JL	94	247	231	32	69	5.3	13	1.8	14%	4.2	100	6	6%	55	150
WM	84	233	67	63	—	4.5	13	2.0	15%	3.8	100	9	9%	58	162
WO	82	312	246	62	50	5.0	13	2.0	15%	4.5	100 50	19 15	19% 30%	33	187
CB	72	246	243	74	36	6.5	13	1.0	8%	4.0	100 50	4 2	4% 4%	70	195
BQ	82	185	130	56	69	5.2	13	3.4	26%	4.1	100 50	12 4	12% 8%	48	202
TJ	84	174	140	108	102	3.7	13	3.6	28%	2.7	100	50	50%	20	165
TS	83	264	97	62	71	4.8	13	0.9	6%	3.8	100	5	5%	63	160
ET	80	282	222	88	66	5.0	13	2.2	17%	4.2	100	17	17%	23	125
Mean	84	244	187	95	69	4.7	—	2.3	18.1%	3.9	—	17.1	17.1%	41	163
Standard Error	2	14	27	31	6	0.3	—	0.3	2.7%	0.2	—	4.6	4.6%	7	9

TABLE 6. *Average Daily Changes in Elemental Balance**

Patient	Δ N (gm)	Δ P (gm)	Δ Ca (gm)	Δ Mg (gm)	Δ Na (meq)	Δ K (meq)	Δ Cl (meq)
MH	5.60 ± 0.4	.05 ± .03	.82 ± .12	.09 ± .01	38 ± 12	(20 ± 10)	35 ± 14
AR	.28 ± .29	.01 ± .07	.04 ± .01	.01 ± .01	(38 ± 10)	14 ± 4	(15 ± 15)
JL	.30 ± .15	.05 ± .03	.04 ± .01	—	17 ± 7	2 ± 4	(41 ± 8)
WM	1.31 ± .15	.01 ± .02	.08 ± .01	.03 ± .01	16 ± 5	10 ± 1	(.7 ± 4)
WO	(.30 ± .30)	(.19 ± .06)	(.02 ± .01)	(.14 ± .01)	7 ± 7	7 ± 1	21 ± 2
CB	2.90 ± 0.50	.40 ± .03	.27 ± .01	(.05 ± .02)	15 ± 4	42 ± 2	18 ± 3
BQ	(.08 ± .28	.09 ± .03	(.08 ± .01)	.01 ± .03	30 ± 4	4 ± 5	25 ± 8
TJ	4.90 ± 0.20	.02 ± .02	(.10 ± .01)	.03 ± .01	16 ± 7	8 ± 1	(24 ± 7)
TS	3.78 ± 0.41	.25 ± .06	.11 ± .02	.08 ± .01	3 ± 6	9 ± 2	(6 ± 17)
ET	2.60 ± 0.60	.42 ± .02	.37 ± .02	.02 ± .01	9 ± 8	19 ± 2	8 ± 8
Mean	+2.13	+0.11	+0.15	+0.01	+11.3	+9.5	+2.0
Standard Error	0.38	0.06	0.02	0.01	6.7	5.1	7.6

*Figures represent daily average ± Standard Error: Numbers in parentheses represent negative values

bacteria present in the jejunum appears to be significantly increased after total gastrectomy. *Anaerobic* counts ranged from 10^5 to 10^{10}/cc in our patients. Microorganisms identified included Bacteroides sp., Clostridia, Veillonella sp., Lactobacilli, and yeasts. Streptococci and *E. coli* were also recovered.

Specimens of jejunal mucosa obtained by the Carey capsule were stained with hematoxylin and eosin. All 10 patients exhibited normal histologic features during light microscopy. Moderate lymphocytic infiltration in the submucosa was noted in two patients. In three additional cases a portion of the specimen was also examined by scanning electron microscopy (Fig. 3). At very high magnification, a qualitative decrease in the number and size of the microvilli was observed.

Fasting small intestinal aspirates revealed the presence of both unconjugated and conjugated bile salts in all 10 cases. Deoxycholic and chemodeoxycholic acids were present in each case, and proved to be the only free bile acids identified in these patients. These findings are summarized in Table 7.

Transit Time. While more subjective than other methodologies described in this report, evaluation of pouch size, emptying time, intestinal transit time, and small bowel mucosal pattern was qualitatively informative.

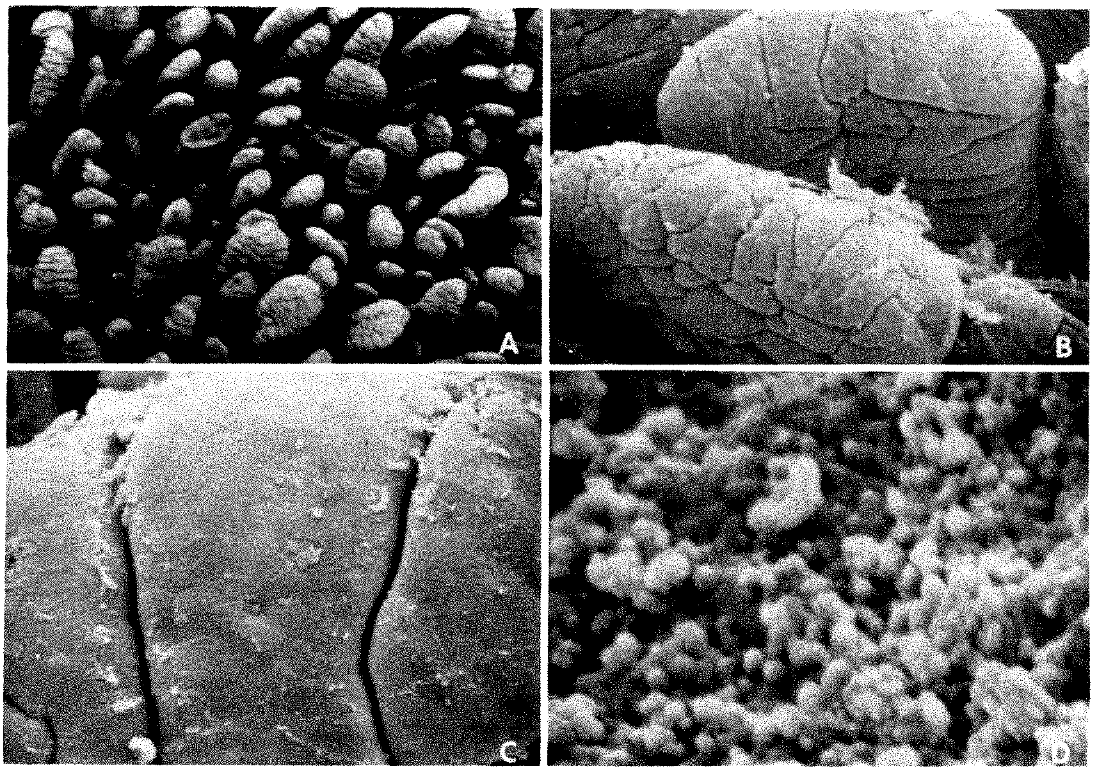

FIG. 3. Micromorphology of jejunal mucosa by scanning electron microscopy. Villi appear normal at × 30 (A), × 250 (B), and × 1000 (C). At × 30,000, a subjective decrease in the size and number of microvilli is noted (D).

TABLE 7. *Jejunal Bile Salt Patterns, Anaerobic Bacterial Counts, and Histology After Total Gastrectomy*

	Bile Salts		Bacterial Count	Jejunal Histology
Patient	Unconjugated	Conjugated	Anaerobes/cc	Light Microscopy
MH	DC;CDC	TC;TDC;TCDC;GC	10×10^6	Villi preserved; lymphocytic infiltration above muscularis mucosa
AR	DC;CDC	TC;TDC;TCDC;GC	73×10^5	Villi preserved; mild increase in lymphocytes in sub-mucosa
JL	DC;CDC	TC;TDC;TCDC;GC	30×10^6	Normal jejunum
WM	DC;CDC	TC;TDC;TCDC;GC	37×10^7	Normal jejunum
WO	DC;CDC	TC;TDC;TCDC;GC	10×10^8	Normal jejunum
CB	DC;CDC	TC;TDC;TCDC	44×10^7	Normal jejunum
BQ	DC;CDC	TC;TDC;TCDC;GC	30×10^7	Normal jejunum
TJ	DC;CDC	TC;TDC;TCDC	10×10^6	Normal jejunum
TS	DC;CDC	TC;TDC;TCDC	10×10^6	Normal jejunum
ET	DC;CDC	TC;TDC;TCDC;GC	10×10^{10}	Normal jejunum

Key: DC—Deoxycholic; TDC—Taurodeoxycholic; CDC—Chenodeoxycholic; TCDC—Taurochenodeoxycholic; TC—Taurocholic; GC—Glycocholic.

In the 7 patients with Hunt-Lawrence reconstruction the barium filled pouch size averaged 6 cm x 16 cm. If the configuration of the pouch can be approximated by a cylinder, these dimensions correspond to a reservoir with a volume of 400-500 cc.

Transit time of the barium column to the right colon ranged from 30 minutes to 5 hours, averaging 2 hours. This was not significantly different from normal controls. Further, there was no difference in intestinal transit time between those with pouch reconstruction and those without ($P>0.10$).

Findings of segmental small bowel dilatation, barium flocculation, mucosal edema, and altered transport evident in 5 patients during the intestinal transit study were interpreted by our radiologists as evidence for malabsorption. However, based upon the results presented in Table 5, the radiologic diagnosis of malabsorption was subsequently proved to be correct in only 3 of 5 in-

TABLE 8. *Summary of Previous Absorption Studies in Patients With Benign Disease Undergoing Total Gastrectomy*

Author-Year	Duration of Metabolic Period (Days)	Type of Anastomosis	Fat Intake (gm/day)	Coefficient of Fat Malabsorption	Nitrogen Intake (gm/day)	Content of Nitrogen in Stool (gm/day)	Coefficient of Nitrogen Malabsorption
Breitenbach, 1929	3	N S	138	6%	—	N D†	—
Farris et al., 1943	3	N S	89	12%	14	0.8	5%
MacDonald et al., 1947	3	N S	40-60	15%	—	N D	—
Brazda, 1950	3	N S	137	7%	—	N D	—
Brain et al., 1951	3	N S	50	25%	—	N D	—
	3	N S	50	18%	—	N D	—
	3	N S	50	11%	—	N D	—
Kelly et al., 1954	3	EJ:JJ	80	6%	12	1.1	9%
	3	ED	80	12%	12	1.8	15%
	3	EJ:Roux-y	80	21%	12	0.3	2%
	3	EJ:JJ	80	13%	12	2.1	17%
	3	EJ;JJ	80	6%	12	0.5	4%
	3	EJ:JJ	80	20%	12	1.0	8%
Brintnall et al., 1956	N S*	EJ:JJ	134	3%	18	1.5	8%
Schwartz et al., 1956	3	N S	72	14%	10	2.0	20%
	3	N S	99	24%	22	2.5	11%
Adams, 1967	7	EJ	100	21%	—	N D	—
	7	EJ	100	12%	—	N D	—
Scott et al., 1968	3	H-L	50-150	5%	13-25	2.4	9-18%
	3	H-L	50-150	20%	13-25	2.6	10-20%
	3	H-L	50-150	6%	—	N D	—
	3	H-L	50-150	10%	13-25	1.0	4-7%

Key: EJ—Esophagojejunostomy in continuity; EJ:JJ—Esophagojejunostomy with Enteroanastomosis (Braun); EJ:Roux-y—End-toEnd Esophagojejunostomy with Roux Anastomosis; HL—Hunt-Lawrence pouch with Roux Anastomosis

*Not stated

†Not done

TABLE 9. *Comparison of Nutritional Parameters in Pouch vs Non-pouch Reconstruction*

	Type of Reconstruction Hunt-Lawrence	 No Pouch
Numbers of Patients	7	3
Smorgasbord (% RDA)		
Caloric intake	125	130
Carbohydrate	172	275
Fat	148	158
Protein	181	175
Coefficient of malabsorption		
Fat	10.6%	31.0%
Protein	15.9%	23.3%
Daily protein balance (gms)	+2.3	+1.6
Relation to ideal body weight	87%	81%
Dumping symptoms	3/7	0/3
Number of daily meals	4.7	3.6
Deconjugated bile salts present	7/7	3/3
Anaerobic bacteria present	7/7	3/3
Jejunal histology	Normal	Normal
Intestinal transit (minutes)	195	180

stances. In addition to the 2 false positive diagnoses of malabsorption, 3 other studies regarded as radiographically normal were done in patients with subsequently documented malabsorption. Diagnosis of malabsorption by these radiologic criteria appears unreliable.

Previous Absorption Studies. During a careful search of the literature, only 22 patients could be found who had undergone absorption studies after total gastrectomy for benign disease (Table 8). The specific type of reconstruction was not specified in 9 of these 22 patients. Another 9 had undergone varying types of esophago-enteric anastomoses without pouch reconstruction, while 4 patients with Hunt-Lawrence pouch reconstruction had been studied. Malabsorption of fat ($>10\%$ of ingested fat) occurred in 69% (15/22), accounting for an average loss of 13% of ingested fat for the entire group. Nitrogen wasting (>2.0 gm/day) occurred in 42% (5/12) but nitrogen loss averaged only 1.6 gm/day for all patients. Since these values did not differ significantly from the values for fat and protein malabsorption reported in this paper ($P>0.10$), the data were combined. Fat malabsorption in the combined series occurred in 66% (21/32) while nitrogen malabsorption was noted in 45% (10/22).

When the coefficient of fat malabsorption of the 11 combined patients with Hunt-Lawrence reconstruction was compared to that of the 12 patients without pouch reconstruction for whom values were reported, the difference was not significant ($P>0.10$). Further, in those patients with available data, the degree of protein malabsorption was not found to be significantly different in 7 patients with pouch reconstruction compared to 10 patients without pouch reconstruction ($P>0.10$). Analysis of the specific type of non-pouch reconstruction was not considered meaningful due to the small numbers involved.

Comparison of Nutritional Parameters in the Present Study. Despite our pre-study bias favoring Hunt-Lawrence pouch reconstruction, none of the parameters investigated (Table 9) were found to be significantly different between those patients with Hunt-Lawrence reconstruction and those without pouch reconstruction ($P>0.05$ in all cases). Of particular interest is the observation that during the hospitalized study period, both groups exceeded RDA caloric requirements as a measure of total intake, and were in positive nitrogen balance. Further, the construction of a pouch did not significantly improve absorption nor result in a lower incidence of dumping symptoms.

Discussion

Proper nutrition initially requires the *availability* of the 5 essential foodstuffs; proteins, fats, carbohydrates, vitamins, and minerals. While access to these nutrients is necessary, it is equally important that proper amounts of these foodstuffs be *ingested,* that *digestion* and *absorption* proceed in a normal fashion, and that *incorporation* and conversion of these foodstuffs into tissue and energy sources occurs.

Malnutrition is most commonly recognized as clinically evident weight loss. Significant weight loss after total gastrectomy has been noted by many observers.[3,10,25,29] Kelly and his associates reported the average postoperative weight loss to be 24% in a group of 16 patients and that only one-third were able to achieve Ideal Body Weight after surgery.[20] In an extensive review of 182 cases of total gastric resection, Adams found that only 10.5% had regained their pre-illness body weight.[1] Nevertheless, since some patients did achieve Ideal Body Weight and a few regained pre-illness weight, significant weight gain after total gastrectomy, although uncommon, has been demonstrated to be *physiologically possible.*

The underlying cause of the malnutrition leading to the observed weight loss has been controversial. Several workers have felt that malabsorption is the primary factor responsible for postoperative malnutrition,[3,24] while others have expressed doubt that malabsorption alone could account for the loss of weight.[10,20] Lawrence and his associates were unable to find any significant correlation between body weight and malabsorption of nitrogen and fat.[22] Several other investigators have suggested that the major cause of weight loss after total gastrectomy might be inadequate caloric intake.[2,6,20,31] Unfortunately, since total gastric resection has historically been reserved for patients with gastric malignancy, it has not been possible to reliably separate the effects on body weight of the procedure *per se* from the concomitant effects of malignancy.

None of the 10 patients reported in this study undergoing total gastrectomy were able to attain their "usual" pre-surgical body weight. Further, although 5 patients were able to achieve 90% of the minimum standard of Ideal Body Weight, only one subject actually exceeded this value. Weights in these patients stabilized at a new level, averaging 15% lower than Ideal Body Weight. In the absence of demonstrable malignancy, the failure of these patients to regain significant amounts of body weight after surgery seems directly attributable to the operative procedure of total gastrectomy. Why should this procedure limit the ability of these patients to achieve even so modest a goal as Ideal Body Weight?

Examination of the smorgasbord data presented in this paper establishes the fact that while under controlled hospital conditions, these patients *can* take in a well-balanced diet sufficient in carbohydrates, fats, proteins, vitamins, and minerals for proper nutrition. Total caloric intake, as well as the specific intake of carbohydrate, fat, and protein, exceeded 100% of Recommended Dietary Allowances for sex and age. These data conclusively demonstrate that these patients are *physiologically capable* of caloric intake sufficient to result in weight gain in the absence of significant malabsorption. While several authors have felt that intake is necessarily restricted in those patients with dumping syndrome,[2,10,20,22] only one of our 3 patients with symptoms of dumping was unable to meet or exceed Recommended Dietary Allowances during the smorgasbord period. The balance data also support the feasibility of weight gain. The positive nitrogen balance (+2.42 gm/day), along with the positive mineral balances, suggests that these patients can incorporate nutrients into new tissue formation. Positive nitrogen and elemental balances have been found in three other patients studied with balance techniques after total gastrectomy for benign disease.[6,28]

However, merely establishing the physiologic capability of these patients to achieve positive balance does not necessarily imply that inadequate intake is not a factor in postoperative malnutrition. Data from individual dietary histories, while qualitative, suggest that these patients do not take in sufficient nutrients when returned to their home situations. In reviewing the dietary histories of 19 patients after total gastrectomy, Adams found the average daily caloric intake to be 2100 Kcalories.[2] Using similar techniques Roberts and his co-workers[27] reported an average caloric intake of 1800 Kcal, noting that only 3 of the 20 patients studied had caloric intakes greater than 2000 Kcalories per day. The possible contribution of residual malignancy to these observations of low caloric intake in the home environment is unknown. When the patients in the present study returned home, the average daily caloric intake declined to 2050 Kcal. At this level of caloric intake only 85% of the RDA for the maintenance of Ideal Body Weight is being met. The decline becomes even more striking when compared to the smorgasbord values during hospitalization. There would appear to be little remaining doubt that inadequate intake is a major factor in the common inability of patients to gain weight after total gastrectomy.

In all likelihood, the demonstrated reduction in dietary intake in the home environment is multifactorial. In view of the more than adequate caloric intake during hospitalization, neither limited capacity nor fear of dumping are acceptable explanations. Lack of appetite, absence of hunger sensations, lack of personal initiative or discipline, economic considerations, or psychic disturbances could contribute to reduced intake. The role of socioeconomic factors is more significant than previously realized in predisposing these patients to malnutrition.

Malabsorption of ingested food is another factor capable of contributing to malnutrition. Malabsorption of both fat and protein has been noted to occur in over 50% of patients after total gastrectomy performed primarily for carcinoma.[3,6,10,20,22] A similar frequency of fat and nitrogen malabsorption occurred in our patients and in other patients undergoing total gastric resection for benign disease (Table 8). The mechanisms responsible for the observed malabsorption are of considerable therapeutic interest.

Previous bacteriologic studies of the human jejunum have shown scant numbers of microorganisms when gastric acid is produced and intestinal motility is unimpaired.[14] As gastric acidity is reduced, bacteria normally found in the colon proliferate in the stomach and proximal small bowel, their numbers approaching those found in patients with intestinal stasis syndromes.[9] However, although patients with pernicious anemia may have intestinal bacterial overgrowth, few have malabsorption.[7] While absolute numbers of bacteria present in the small intestine are important, the types of microorganisms recovered also determine the development of intestinal overgrowth syndromes. Gorbach and Tobaqchali have shown particularly that the presence of anaerobes in the jejunum is definitely abnormal.[13]

The bacterial overgrowth syndrome is thought to be responsible for many aspects of malabsorption. In 1966 Drasar and his associates showed that Bacteroides sp. were capable of deconjugating human bile salts.[8] Deconjugation of bile salts by anaerobic bacteria prevents micelle formation by reducing the effective concentration of conjugated bile salts, which impairs the transport of hydrolyzed fat across the intestinal mucosa. The resultant lack of fat absorption is manifested as steatorrhea. It has been subsequently shown that Clostridia, Lactobacilli, and anaerobic Streptococci also deconjugate bile salts, but to a lesser degree.[13] Protein malabsorption may also result from anaerobic bacterial overgrowth, presumably by bacterial deamination and diversion of dietary protein nitrogen to urea.[7,19] Intestinal bacteria also use vitamins and other nutrients, including the carbohydrate D-xylose used as a test of absorption.[7] Bacterial use of D-xylose would result in abnormally low urine concentrations. Four of our 10 patients did exhibit abnormal absorption of D-xylose in the absence of renal disease and despite normal intestinal biopsies. Bacteria also bind the vitamin B_{12}—intrinsic factor complex and prevent the absorption of B_{12} even in the face of sufficient intrinsic factor.[13] Every one of our patients exhibited abnormally low absorption of vitamin B_{12} during a second stage Schilling test.

Significant anaerobic colonization of the jejunum after total gastrectomy has been demonstrated in this report. In our patients with surgical achlorhydria, Bacteroides sp., Clostridia, Veillonella sp., and Lactobacilli were present in numbers ranging from 10^5 to 10^{10}. The observed fat and nitrogen malabsorption is at least partially a result of the overgrowth of anaerobic bacteria. Eradication of anaerobic intestinal overgrowth with antibiotics has been associated with a decrease or disappearance of free bile acids and a reduction in steatorrhea in patients with jejunal diverticulosis and blind-loop syndromes.[30] While it is likely that antibiotics will prove equally effective for bacterial-induced malabsorption of fat and protein in patients after total gastrectomy, further studies are in progress.

Pancreaticobiliary insufficiency represents another possible mechanism of malabsorption in these patients, but is of unknown clinical significance. In the extreme case of *absolute* pancreatic insufficiency represented by total pancreatectomy, malabsorption of fat and protein is a constant result.[26] Presumably, lesser degrees of pancreatic insufficiency should result in correspondingly less malabsorption of protein and fat. Pancreatico-cibal asynchrony, a *relative* pancreatic insufficiency, could result in those patients whose reconstruction excludes the passage of food through the duodenum. It has been proposed that when ingested food does not traverse the duodenum, the output and mixing of bile and pancreatic enzymes with ingested food is delayed beyond the time necessary for proper digestion.[23] Without emulsification and specific hydrolysis by pancreatic peptidases and lipase, malabsorption would result. Additional studies in 2 of our patients with fat and protein malabsorption support the contention that an uncharacterized pancreatic insufficiency exists in some of these patients. Adding exogenous pancreatic enzyme replacement reduced fat malabsorption 40% in one patient. Lundh[23] has reported a similar reduction in steatorrhea after total gastrectomy with exogenous pancreatic replacement. On another occasion fat which has been previously digested by pancreatic lipase was substituted for ordinary dietary fat, and resulted in a 26% decrease in fat malabsorption when compared to the balance diet. While these studies suggest that pancreatic insufficiency is of some importance, they do not in themselves distinguish between absolute and relative pancreatic insufficiency. Further, although simulating endogenous pancreatic hydrolysis produced a notable improvement, malabsorption was not eliminated. The relative contributions of pancreatic insufficiency and bacterial overgrowth to malabsorption after total gastrectomy remain to be determined by further studies.

Carbohydrate absorption can not be tested by objective absorption or balance techniques because of substrate use by coliform microorganisms. The pattern of early relative hyperglycemia and delayed hypoglycemia displayed by our patients in response to glucose tolerance testing is well recognized[2,6,24,25] and reflects rapid jejunal absorption and a subsequent relative insulin excess.

In view of the consistently normal small bowel histology and intestinal transit times reported in this study and by others,[2,25] mucosal absorptive defects and accelerated intestinal transit seem unlikely mechanisms of malabsorption in the usual case. The qualitative decrease in the number and size of the jejunal microvilli demonstrated by scanning electron microscopy is in keeping with anaerobic bacterial overgrowth,[7] but the exact significance of this observation is unknown.

Whatever the mechanisms of the observed malabsorption prove to be, it is necessary to estimate the relative importance of malabsorption in promoting postoperative malnutrition. Since the magnitude of caloric loss from the balance diet in our patients with malabsorption can be calculated to have ranged only from 117-530 Kcal/day, such losses could easily be covered by increasing caloric intake. In fact, voluntarily increased caloric intake averaging 125% of RDA was a prominent feature of the smorgasbord diet. It would seem that the contribution of malabsorption in reducing caloric availability below ideally required levels is dependent upon the caloric intake. Patients with malabsorption may make up a caloric loss by greater intake than would otherwise be required for positive balance in the absence of malabsorption. Under these conditions, however, if for any reason intake could not be increased, malabsorption might then become a significant factor in the production of malnutrition.

In an effort to improve nutrition after total gastric resection, several surgeons have advocated the construction of enteric reservoirs, presumably capable of permitting comparative increases in food intake and decreasing dumping symptoms by enlarging storage capacity. Herrington has recently reviewed the indications and techniques of various pouch reconstructive procedures.[18] Although there seems to be little doubt that pouch reconstruction serves to decrease the sensation of early satiety, whether this method of reconstruction actually results in the proposed long term benefits of greater weight gain, reduction in the degree of malabsorption or significant decrease in postoperative sequellae when compared to other forms of reconstruction is subject to question. Few objective studies have been done.

Hays and Clark[17] were able to show an average caloric intake of 3350 calories from a smorgasbord diet in 4 patients subjected to their triple lumen jejunal pouch after total gastrectomy for carcinoma. While these patients weighed an average 90% of their "usual" weights, the pouch did not protect against documented protein and fat malabsorption. Considerable disenchantment with transverse colon pouches was expressed by Gerwig who reported persistent anorexia, malnutrition, eructation, regurgitation, and esophagitis in a 5-year followup study of 4 patients.[12] Recently Scott and his co-workers have been persuasive advocates of Hunt-Lawrence pouch reconstruction.[29] Eight patients with this type of reconstruction followed 3 to 5 years after surgery underwent extensive metabolic studies. Although mild protein and fat malabsorption persisted, it was concluded that the overall results of Hunt-Lawrence reconstruction were superior to previously employed techniques of reconstruction.

In the only previous study evaluating both pouch and non-pouch reconstruction after total gastrectomy, Moreno reported findings in 5 patients with a double lumen jejunal pouch interposed between the esophagus and duodenum, compared with observations in two patients with esophagojejunostomy.[25] All of the patients were studied within 2 years of surgery and each had undergone resection for carcinoma. There were no statistically significant differences in postoperative weight gain, in fat or nitrogen absorption, or in the incidence of dumping. The present study compared the nutritional consequences of pouch versus non-pouch reconstruction in 10 patients without demonstrable malignancy. From an analysis of the patients reported in this study, the amount of food ingested and the relation to Ideal Body Weight was similar between the two methods of reconstruction, the degree of malabsorption was comparable, and use of nutrients as reflected by positive nitrogen balances was equal. In addition, since postoperative symptomatology was not improved, the rationale for continuation of this method of pouch reconstruction seems unclear. While only the Hunt-Lawrence pouch was evaluated in this study, in the absence of other comparative data, the premise that other types of pouches differing slightly in technique, size, or location will prove to be nutritionally superior methods of reconstruction requires objective verification.

Acknowledgment

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DISCUSSION

DR. ROBERT M. ZOLLINGER (Columbus, Ohio): The authors have made a real contribution by emphasizing the responsibility of the surgeon in sustaining an active interest in the patient's nutritional trend after total gastectomy. For many years we have been impressed on how well patients have done after total gastrectomy for the ulcerogenic islet cell tumor in comparison to the patients having total gastrectomy associated with carcinoma of the stomach.

As a policy, we have tried to get our patients admitted to the hospital three months, six months or double the time between admission for at least a year, and then on a yearly basis.

(Slide) In studying 16 of these patients having total gastrectomy whom we have watched rather carefully for 1 to 21 years, all of them had the Roux-en-Y procedure. These patients have been observed for 1 to 21 years and you will see that 75% have hypergastrinemia and maintained their ideal body weight. To our surprise, 63% were above ideal body weight, and one third who were below ideal body weight had recurrent tumor as manifested by high gastrin levels following infusion studies of calcium, secretin or magnesium sulfate or by angiogram. Or, they had stenosis of the esophageal jejunum as shown by barium studies.

(Slide) We weren't too surprised that of the seven people living longer than five years, three-fourths of them had hypergastrinemia but we do not have a level on two others. But we began to feel that practically all these patients, even years afterwards, will have a sustained hypergastrinemia, and 85% of these patients were at their ideal body weight and one individual was 15% below ideal body weight. The later case had an anastomotic stenosis that required surgical correction. He has continued to live, however, on cashew nuts and we find him a challenging nutritional problem!

And finally, I would raise the question of whether a modest elevation in gastrin levels insures a better long-term nutritional status.

We have long felt that hypergastrinemia might play a role in treating these patients who have proven islet cell tumors who certainly seem to have sustained a good ideal weight. This discussion of calories, of course, eases my conscience when I think about the number of times I've asked the Board of Surgery about the number of grams of protein in an egg or a glass of milk!

DR. THOMAS C. MOORE (Torrance, California): This is certainly a very interesting and important paper concerning nutritional aspects of total gastrectomy for benign disease.

I wish to comment upon the results of total gastrectomy for benign disease in a very demanding crucible of the pediatric patient. A number of years ago, I carried out a near total gastrectomy on a two-day-old infant for spontaneous necrosis of virtually the entire stomach with perforation and a massive amount of free air in the peritoneal cavity on roentgen examination.

This infant recovered and grew and developed normally in the following years. His growth was comparable to a first cousin born at the same time.

This finding stimulated a review of the world experience with gastrectomy in the pediatric age group by surveying both the Canadian, American and world leaders in pediatirc surgery. I was able to accumulate 114 cases of gastrectomy in the pediatric age group. This data was published in *Annals of Surgery* in July 1965.

From this group of patients, there were three cases of total gastrectomy and all of them grew and developed normally. One very interesting patient was provided by Professor Jan Louw of South Africa. This patient of about ten years of age had massive obstructing gastric granuloma with marked malnutrition. In the postoperative period, following total gastrectomy, this patient not only maintained the prior weight, which was a starvation weight, but actually gained 30 pounds in about two or three months.

I would like to ask Dr. Bradley if he has found any difference in the results of the patients who had a Zollinger Ellison syndrome. I think this syndrome accounted for six out of the ten patients in his report. Dr. Friesen commented earlier that this was a persisting and complicated type of syndrome with multiple organ involvement frequently.

I would also like to make one final comment about the possible additional management for some of these patients—and this also is in a sense a delayed discussion as well as of Dr. Friesen's paper.

The Z-E syndrome patients belong to the class of patients with foregut endocrine polypeptide-secreting APUD cells (amine-precursor-uptake and decarboxylation) reported earlier by Dr. Friesen. The Z-E syndrome lesion cells may involve complex biochemical reactions related to decarboxylation of amino acids in addition to polypeptide production.

The hydroxy tryptophan, histidine and dopa which may be decarboxylated to serotonin, histamine and dopamine might be involved in some of the related symptoms and metabolic effects. These vasoactive substances also are important neurotransmitters.

As Dr. Friesen commented, they derive embryologically from the neural crest, involve the foregut and are involved with a number of important metabolic activities, including potent stimulation of cyclic AMP.

It is theoretically possible that agents which inhibit decarboxylation of the above cited amino acids may be of value therapeutically in some of these patients on a long-term basis.

DR. WALTER LAWRENCE, JR. (Richmond, Virginia): I though I would like to rise, not to defend what I call the "Scott pouch," but to make the point that I think that Dr. Bradley has really, in a sense, placed the wrong emphasis on the data he has presented today.

In the late 50s, Tom Randall, Parker Vanamee and I presented before this society some of our metabolic data after total gastrectomy in cancer patients, but I'm not sure that these subjects were so different from the ones reported today. We were disappointed to find out after many dollars of metabolic study, and I think this is all Dr. Bradley has actually shown us today, is that you don't gain weight if you don't eat!

In other words, I think post-gastrectomy malabsorption situation which we studied as a great "mystery," was proven then and is again proven today, as being of no significance. Significant malabsorption doesn't occur in these patients so that using this as an index for comparing variations in reconstruction seems in a way to be inappropriate. Any approach that you use that makes people eat better, whether it be a modification of their diet so you have less hyperosmolar meals, or whether you reconstruct in such a way as you might prefer to make them tolerate a larger volume diet, will make their nutrition better. I think his data has made this point to some extent in this presentation, but I was fearful there was too much emphasis on the slight differences in malabsorption. I think this has been long settled as being an unimportant feature of malnutrition after gastrectomy.

DR. DAVID TILSON (New Haven, Connecticut): It was mentioned that the jejunal villi were normal. Did you measure them with a micrometer? A small decrease in the length of the villus, because of the geometry of a cylinder, can result in a rather large decrease in absorptive surface.

I would like to advance a speculative note that occurred to me as I heard Dr. Zollinger say that the hypergastrinemic patients tend to do very well after total gastrectomy. We have a hunch that gastrin may be a hormone that stimulates intestinal adaptation in short gut syndrome, and some preliminary data from our laboratory support that notion. Conversely, in hypogastrinemic patients a contributory factor to the malabsorption may be a loss of the trophic effect of gastrin on the intestinal mucosa.

DR. E. L. BRADLEY, III (Closing discussion): Dr. Zollinger, we do agree with you that repeated evaluations of these postoperative patients are quite necessary. It was remarkable to us as we looked over our data the number of people developing one or more nutritional deficits with time. A number of defects appear in these patients which, if sought, can prevent many of the various deficiency syndromes.

The ability to maintain normal growth and development in a pediatric population after total gastrectomy was noted by Dr. Moore. His good results are similar to those results from the pediatric patients in the Zollinger-Ellison Tumor Registry, reported by Dr. Stuart Wilson. Dr. Moore, we were unable to find any difference in any of our results between groups of patients with and without Zollinger-Ellison syndrome. Your suggestion that agents inhibiting decarboxylation might be of value in the control of APUD tumors is quite interesting and worthy of further study.

Dr. Lawrence was concerned that we might have misinterpreted our data in that too much emphasis was placed on malabsorption. While the manuscript may be clearer than perhaps I have been today, the data presented support several statements. In agreement with Dr. Lawrence, but documented for the first time, is the fact that most patients weigh less after total gastrectomy simply because of inadequate intake. As a corollary to this observation, we have shown that while pouch reconstruction can reduce early satiety to some degree and therefore increase the volume of intake at any given sitting, over several days there is no difference in intake between methods of reconstruction. Secondly, malabsorption occurs in all of these patients but is only occasionally severe. We hope that the demonstration of anaerobic overgrowth will have some therapeutic importance.

Drs. Tilson and Zollinger have commented upon the possible beneficial effects of high gastrin levels, presumably acting as a trophic agent upon the intestinal mucosa. We were not unaware of this possibility, but could find no difference between the ZE patients (all of whom continue to have elevated postoperative gastrins) and the other patients undergoing total gastrectomy for benign diseases. Dr. Tilson, we have no quantitative data to support our contention that the jejunal villi were normal under light microscopy. However, in the manuscript we show what we consider to be a qualitative decrease in both size and number of microvilli under scanning electron microscopy.

Revascularization in Treatment of Mesenteric Infarction

J. J. BERGAN, R. H. DEAN, J. CONN, JR., J. S. T. YAO

This study compares results of primary revascularization with primary intestinal resection in treatment of acute mesenteric artery occlusion in 48 surgical patients. All cases were verified by surgical exploration, angiography or autopsy. Fifteen occlusions were caused by mesenteric thrombosis and 33 by superior mesenteric artery embolization. Primary revascularization was done in 6 of 15 patients with arteriosclerotic mesenteric thrombosis. Total bowel salvage was achieved in 4 patients but no patient with mesenteric thrombosis treated by any method survived long term. Primary embolectomy was done in 11 patients with superior mesenteric artery embolization. Total bowel salvage was achieved in 8 patients. Three of 11 patients died. Primary exploration and/or resection was done in 11 patients; 9 died. All 11 unoperated patients died. A continuation of attempts at mesenteric revascularization is advocated.

REVASCULARIZATION BY EMBOLECTOMY, endarterectomy or bypass is accepted as appropriate treatment of acute arterial occlusion in the extremities. However, a similar philosophy regarding acute mesenteric vascular occlusion has not developed. The reasons for avoidance of revascularization as primary treatment of acute bowel infarction are not clear but probably relate to lack of understanding of the need for precision in diagnosis, lack of appreciation of the nearly 100% mortality of primary resectional therapy, or a fatalistic acceptance of the lethal nature of the condition.

An understanding of the ability to differentiate between the syndromes of mesenteric artery thrombosis, mesenteric embolization, non-organic arterial occlusion, mesenteric venous occlusion, and other causes of splanchnic vascular occlusion is a product of the last two decades of surgical experience. Prior to this, the hypothesis regarding the possibility of restoring intestinal blood flow with resultant bowel salvage was untested.

This report summarizes experience in attempting revascularization as primary treatment of mesenteric infarction. The concurrent surgical experience obtained in the same medical setting over the same time span using the conventional and acceptable non-revascularization approach to this problem is detailed for comparison. The consecutive cases described were treated over a time period during which various syndromes of acute mesenteric arterial occlusion were defined, intestinal arteriography became an acceptable diagnostic technique, and knowledge regarding systemic effects of intestinal revascularization emerged.

From the Department of Surgery of the Northwestern University School of Medicine, the Department of Surgery of the Vanderbilt University School of Medicine and the Blood Flow Laboratory of the Northwestern University-McGaw Medical Center, Chicago, Illinois

Patient Population

During the 19-year period from 1955 through 1974, 48 patients, the subject of this report, were treated on surgical services of the Northwestern University-McGaw Medical Center hospitals. All of these patients had acute intestinal infarction due to superior mesenteric artery occlusion with or without celiac axis or inferior mesenteric artery occlusion. All cases were verified by angiography, surgical exploration, autopsy or, in many instances, a combination of methods. Patients with mesenteric venous thrombosis, steroid induced or treated microvascular occlusive disease, nonorganic arterial occlusion, or mesenteric artery occlusion produced by dissecting aneurysm of the aorta have been excluded from consideration.

Mesenteric Thrombosis

There were 15 patients, 7 men, 8 women, who experienced arteriosclerotic thrombosis of mesenteric vessels sufficient to cause acute intestinal infarction. Although

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Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

TABLE 1. *Cardinal Features of Mesenteric Embolization in 33 Patients*

	Patients
Sudden Abdominal Pain	29
Significant Cardiac Lesion	32
Previous Embolic Event	11
Vomiting	27
Bowel Evacuation	23
Severe Leukocytosis	22

these patients ranged in age from 29 to 76 years, only 3 were under age 50. Treatment was primarily by revascularization in 6 cases with concomitant resection in 3. Six patients were explored surgically primarily to establish diagnosis and/or resect necrotic bowel. Four of these patients sustained intestinal resection, two were merely opened and closed. Three additional patients were moribund on first evaluation and were not operated upon.

Nine patients, 4 treated by primary revascularization, were admitted to the hospital more than 48 hours prior to surgical exploration. In these, the characteristic history was of increasingly severe generalized abdominal pain followed by abdominal distension, nausea, vomiting, passage of loose stools without gross blood, coincident severe leukocytosis, acidosis, and massive elevations of serum LDH, SGOT, SGPT, and CPK with inconsistent hyperamylasemia. Psychiatric consultation was considered in several patients and actually obtained in one because subjective patient complaints of pain were out of proportion to objective findings.

Superior Mesenteric Embolus

Thirty-three patients, 15 men, 18 women, sustained embolic occlusion of the superior mesenteric artery and developed bowel infarction (Fig. 1). Treatment was by primary embolectomy in 11 with associated resection in 2. One patient required a second look operation. Eleven patients were operated upon to resect compromised bowel[8] or establish diagnosis.[3] Eleven patients were not operated upon for various reasons relating to advanced age and/or hopelessly moribund condition.

Table 1 indicates cardinal clinical features in these 33 patients with confirmed superior mesenteric artery embolization. The diagnostic triad of; 1) acute abdominal crisis in a patient with, 2) significant cardiac disease associated with, 3) gastrointestinal emptying was present in two-thirds. Additional characteristics of this syndrome included a history of prior peripheral arterial embolization and leukocytosis greater than 17,000. Both of these latter two features were present in more than one-half of the patients.

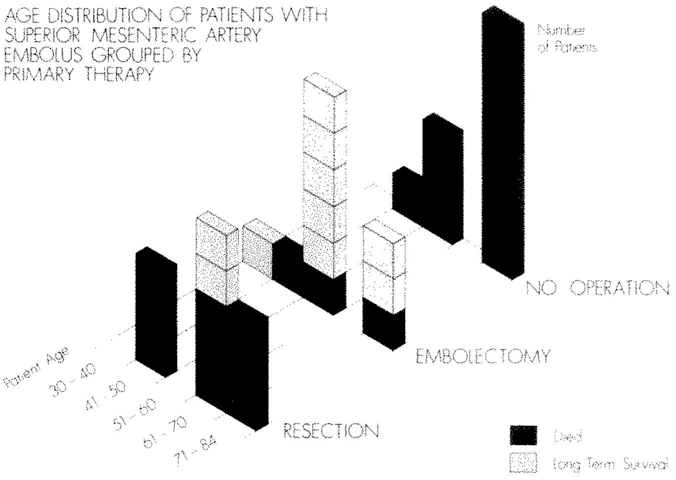

FIG. 1. This graphic display of patients with superior mesenteric artery embolization groups cases according to modality of treatment and indicates those who survived long term.

Treatment and Results

Diagnosis of superior mesenteric artery thrombosis is delayed by the insidious onset of the condition. This is in contrast to classical mesenteric embolization which frequently produces an onset which can be timed precisely. Treatment of mesenteric thrombosis is further disadvantaged by the extensive nature of the bowel ischemia. This frequently affects even the proximal jejunum as well as portions of right colon. In addition, if revascularization is attempted, the procedure is necessarily more complex than simple embolectomy. Because of these 3 differences, it is pertinent to consider separately treatment of the two conditions both of which produce lethal intestinal infarction.

Mesenteric Thrombosis

Three non-operated patients with SMA thrombosis exhibited acidosis, hypotension, profound serum elevations of intracellular enzymes, and leukocytosis at the time of surgical evaluation. All died promptly. One had given a 72-hour history of a developing abdominal crisis which was untreated. Two patients operated upon without revascularization or resection showed necrosis of the entire small bowel and right colon. One demonstrated gastroduodenal and left colon necrosis as well. One died one hour and the other 48 hours after surgical exploration. Four patients sustained intestinal resection without revascularization and all died within 30 days.

Primary revascularization in treatment of mesenteric thrombosis was attempted in 6 patients (Table 2). Two patients underwent attempted revascularization of severely compromised bowel by superior mesenteric thromboendarterectomy. In the first, a proximal blind disobliteration was done, in the second a formal, full scale exposure of the entire upper abdominal aorta was performed as described elsewhere.[3] In one, no bowel viability was achieved. The patient, a 68-year-old woman operated upon in 1962, had a 4-day history of developing

TABLE 2. *Results of Revascularization in Patients with Superior Mesenteric Artery Thrombosis*

Age, Sex	Operation	Survival	Cause of Death	Bowel Status	Associated Disease
69, F	Endarterectomy SMA	12 Hours	Peritonitis	Nonviable	Diabetes Mellitus
63, F	Endarterectomy SMA	5 Hours	Cardiac	Viable	Diffuse Atherosclerosis
73, M	Aortomesenteric Graft	9 Days	Aspiration	Viable	Diffuse Atherosclerosis
68, F	Aortomesenteric Graft	11 Days	Peritonitis	Nonviable	Polycythemia
58, M	Thrombectomy	20 Days	Carcinoma	Viable	Carcinomatosis
59, M	Aortomesenteric Graft	10 Days	Myonecrosis	Viable	Polycythemia

intestinal necrosis which retrospectively was irreversible. In the other, severely compromised bowel extending from duodenum to rectum caused by total occlusion of the celiac axis and superior mesenteric artery was restored to viability by superior mesenteric thromboendarterectomy. The patient, a 65-year-old woman operated upon in 1965, awoke from anesthesia only to die suddenly 5 hours later. Autopsy showed well vascularized bowel.

Two patients were revascularization technical failures. One was treated by attempted thrombectomy and bowel resection, the other by aortomesenteric graft and limited bowel resection. The former, a 57-year-old man with advanced bronchogenic carcinoma and pulmonary thromboembolic disease treated by vena cava clipping, required heparin anticoagulation continuously for 11 months prior to superior mesenteric artery thrombosis. No atheroma was found within the artery and repeated thrombectomy using the Fogarty catheter failed. Intestinal resection was done and the patient died 20 days later. The other technical failure might also be related to coagulopathy. The patient, a 68-year-old woman with known treated but uncontrolled polycythemia rubra vera, was operated upon within 24 hours of mesenteric artery thrombosis and an aortomesenteric graft allowed salvage of all colon and 50 cm of jejunum with 15 cm of ileum. The edges of anastamosed intestine were exceeding well vascularized. Heparin anticoagulation was maintained until the 8th postoperative day. The subsequent clinical course suggested occlusion of the graft, dehisence of the bowel anastamosis, peritonitis, and fatal septicemia.

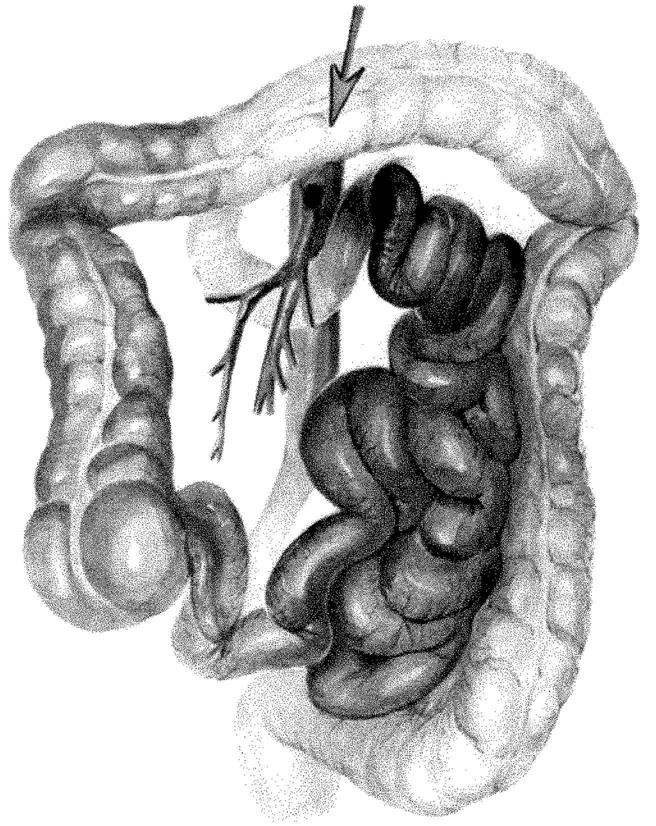

FIG. 2. This drawing indicates the operative situation in acute mesenteric arterial thrombosis. Note severe compromise of the proximal jejunum.

Two other patients, both men, one 59 and the other 73, were early survivors of aortomesenteric grafting with 8 mm dacron tubes. These allowed total intestinal salvage without resection or second look operations. One died on the 10th postoperative day of toxicity from extremity myonecrosis sustained at the time of the aortomesenteric thrombosis. The other died of aspiration pneumonia after oral alimentation was begun on the 5th postoperative day. Present surgical technique is shown in Figs. 2,3 and 4.

Mesenteric Embolus

Eleven patients with confirmed superior mesenteric artery embolization were not operated upon because of late diagnosis, acidosis with and without generalized sepsis or advanced associated cerebrovascular or cardiac disease; all died promptly.

Eleven patients (Table 3) with superior mesenteric artery embolization were operated upon without consideration given to embolectomy or other revascularization. Three were merely closed without further intervention, In each instance gastroduodenal and upper jejunal viability was noted although in one instance bowel necrosis extended to the distal transverse colon. Four patients undergoing intestinal resection survived the primary procedure only to sustain intestinal fistulas. Each of these patients died of septic complications directly related to the intestino-cutaneous fistula.

Two patients survived intestinal resection as primary treatment of the bowel infarction caused by superior

TABLE 3. *Results of Surgery Without Revascularization in Patients with Superior Mesenteric Artery Embolization*

Age, Sex	Delay	WBC	Complication	Result
72, F	6 hrs	11,300	None	Survived
70, M	18 hrs	10,500	None	Survived 4 mon
45, M	18 hrs	20,130	Intestinal Fistula	Died
62, M	24 hrs	14,800	Intestinal Fistula	Died
73, F	24 hrs	17,000	Sepsis	Died
62, F	24 hrs	18,600	Explored only	Died
69, F	26 hrs	15,900	Intestinal Fistula	Died
63, F	30 hrs	42,000	Renal Failure	Died
77, F	36 hrs	30,500	Explored only	Died
49, F	48 hrs	20,000	Explored only	Died
48, M	17 days	30,000	Intestinal Fistual	Died

mesenteric artery embolization. One, a 70-year-old man, survived a 30 cm bowel resection without complication. A superior mesenteric artery branch embolus was found within the surgical specimen. The patient died 4 months later of myocardial infarction. The second survivor of resectional therapy of embolus induced bowel infarction sustained a 120 cm small bowel resection without complication.

Eleven patients (Table 4) with superior mesenteric artery embolization were operated upon with a primary objective of restoring intestinal blood flow. No resection of bowel was necessary in 8. None of these patients required a second look operation. One death from hepatitis occurred in this subset of cases. In this instance the patient was in the hospital with known hepatitis following aortic valve placement. Though bowel viability was restored, the hepatic insult of intestinal ischemia and surgical manipulation was fatal.

Three patients required bowel resection following embolectomy. One sustained the embolic event following cardioversion, and was operated upon 48 hours later when embolectomy was done. A planned second look operation 12 hours later showed need for a massive intestinocolonic resection. The upper jejuno-transverse colic anastamosis healed and the patient survived many difficult weeks of intravenous and oral alimentation. He eventually achieved normal food intake and occupational rehabilitation. One patient dying of respiratory complications following embolectomy and simultaneous bowel resection had experienced ancient massive cerebral infarction, acute myocardial infarction and recent extremity embolization. The third death occurred 26 days following mesenteric artery embolectomy in a 75-year-old man with recurrent femoral and mesenteric artery emboli and severe cardio-respiratory insufficiency. He required bowel resection 21 days after mesenteric embolectomy.

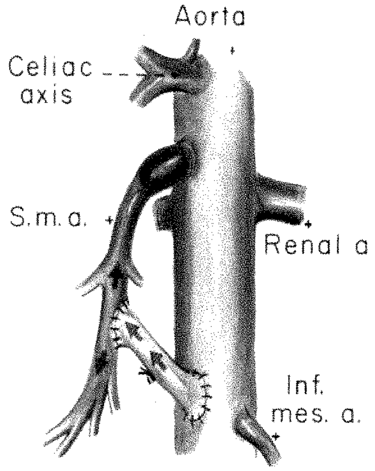

FIG. 3. A short aortomesenteric graft of autogenous saphenous vein, as shown here, or of 6-8 mm dacron is placed preliminary to bowel resection in treatment of acute mesenteric artery thrombosis.

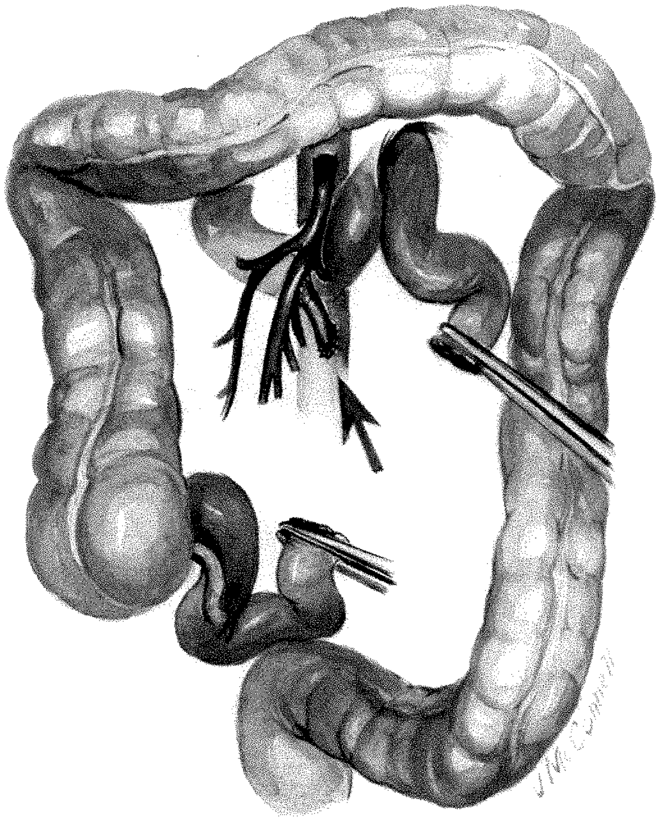

FIG. 4. Following revascularization, and after a 20 to 30 minute waiting time, resection of obviously necrotic intestine is completed and anastamosis performed.

TABLE 4. *Results of Revascularization in Patients with Superior Mesenteric Artery Embolization*

Age, Sex	Delay	WBC	Operation	Result
55, F	6.0 hrs	15,200	No Resection	Success
63, M	8.5 hrs	19,000	No Resection	Success
36, M	12.0 hrs	12,450	No Resection	Success
54, M	12.0 hrs	18,000	No Resection	Success
42, M	24.0 hrs	23,725	No Resection	Died, Hepatitis
62, F	24.0 hrs	18,000	No Resection	Success
73, M	30.0 hrs	17,800	No Resection	Success
82, M	30.0 hrs	14,100	No Resection	Success
60, M	36.0 hrs	28,000	60 cm Resection	Died, Respiratory
52, M	48.0 hrs	20,900	Massive Resection	Success
75, M	26 Days	26,900	60 cm Resection	Died, Late

Historical Resume

In order to assess the results of the present trial of revascularization in treatment of mesenteric infarction, it is necessary to frame an historical perspective. Although Litten in 1875[34] described gross intestinal changes produced by experimental superior mesenteric artery ligature, it was Elliott's 1895[21] report of resectional therapy which had the greatest therapeutic impact. This influenced surgical therapy of this condition for the next half century. Litten's work was confirmed[55] in this country while several anatomic pathologists were showing that multiple mesenteric artery occlusions could be tolerated without symptoms in some patients.[25]

The first breakthrough in improving results of treatment of mesenteric ischemia was Dunphy's prescient observation in 1936 that one-half of the cases studied by him had gastrointestinal symptoms which preceded lethal bowel infarction.[20] Later, Mikklesen re-emphasized the importance of intestinal angina and suggested that occlusion of more than one mesenteric artery was requisite to production of patient symptomatology.[40,41]

Noer pointed out in 1943 that anatomical species differences existed in the mesenteric circulation of dog and man.[44] Lessons pointed out by this study did not prevent later attempts to extrapolate laboratory observations to explain human experience.

The second significant breakthrough in improving results of surgical treatment of acute bowel infarction came from Klass' report in which he succinctly defined the three hallmarks of the syndrome of mesenteric artery embolization.[27,28]

Inevitably, successful superior mesenteric artery embolectomy was performed[50,58] and by the end of 1974 it was possible to summarize results of 49 cases of successful and 20 cases of unsuccessful embolectomy.[14]

Shaw was not only the first to perform mesenteric embolectomy without bowel resection[48] but also among the first to advocate a second look procedure after intestinal revascularization. Others[8,60,61] stressed the lethal import of intestinal fistulas after surgical treatment of bowel infarction and further advocated the second look.

Although Dumont's observation in 1961[19] that seromuscular layers of bowel were resistant to ischemia was important, few took up his advocacy of arterial disobliteration in treatment of arteriosclerotic mesenteric artery thrombosis. In fact, Brittain's 1963 report[16] remains a bench mark in attempted revascularization of thrombosis induced ischemic bowel. His successful treatment of three of four patients by superior mesenteric endarterectomy remains unequalled. Since that time, few cases of attempted acute intestinal revascularization have been published in sufficient detail for analysis.[24,59]

Attempts have been made in research laboratories to define the systemic effects of revascularization of ischemic intestine. These studies assumed particular importance after Mavor's description of 6 cases of mesenteric artery embolectomy or endarterectomy in which there were no survivors.[39] Investigations have stressed importance of intracompartmental fluid shifts, release of histamine, bradykinin, vasodilator polypeptides, platelet aggregating substances, serotonin, substance P, adenine nucleotides, proteolytic enzymes, free potassium ion, myocardial depressant factor, and intramucosal and/or submucosal hemorrhage.[7,10,13,15,18,22,29,30,32,33,35–37,42,43,47,51,52,54,57]

Accompanying these studies have been some excellent investigations to define ultrastructural effects in ischemic intestinal cells.[1,17]

However, the third contribution to care of patients with acute intestinal ischemia has been a realization that the term mesenteric vascular occlusion is archaic. This all-inclusive non-diagnosis has now been replaced by specific terms which suggest exact modalities of therapy. These precise diagnoses include: mesenteric embolization which suggests embolectomy,[2,3,5,12,23] mesenteric thrombosis, which suggests aortomesenteric grafting[14] nonorganic mesenteric arterial occlusion[56,57] which suggests pharmaco- or pharmacoangiographic therapy,[14] and mesenteric venous occlusion which calls for intestinal resection and treatment of the coagulopathy.[38,53]

That a need exists for a better method of treating acute intestinal infarction is indicated in Table 5. This summarizes surgical cases treated in and reported from

TABLE 5. *Mortality of Mesenteric Infarction*

Hospital Reporting	Number of Cases	Mortality
Massachusetts General Hospital[45]	51	95%
Seattle Kings County[46]	56*	100%
University of Pittsburgh[49]	18	96%
Oslo, Ulleval Hospital[31]	22	90%
Medical College of Virginia[62]	21	100%
University of Minnesota[26]	35	88%
Aberdeen Infirmary[39]	71	93%

*Surgical cases only

experienced centers. The dominant approach to this problem was not that of primary revascularization.

Discussion

Experience with this group of 48 cases of acute intestinal infarction shows that many concepts taught regarding acute mesenteric infarction must be modified according to the cause of such infarction. Clearly the most important cause of surgical acute intestinal ischemia is mesenteric embolization rather than thrombosis. Thirty-three of 48 cases in this series demonstrated this as the cause of intestinal necrosis. This is similar to the observation of Liavag who noted 18 cases of mesenteric embolization in 22 patients with mesenteric infarction.[31] In this coterie of cases, a prior history of post-prandial pain, weight loss or other gastrointestinal symptoms would be unexpected. Therefore, in the majority of patients with intestinal infarction remediable by surgical means, as many as 60% of cases, the only significant past history would be that of cardiac disease with or without a previous peripheral embolic episode.

It is important to note that acute occlusion of a single major intestinal artery can produce massive bowel infarction. Coincident blockage of celiac axis or inferior mesenteric artery is not requisite to massive bowel necrosis when the superior mesenteric artery is acutely occluded. Conversely, when two or even all three intestinal arteries are occluded, restoration of flow through one may produce total reversal of bowel ischemia. Since the superior mesenteric artery is the more accessible of the two vessels which supply the midgut, it is the logical conduit to reopen.

Once precision in diagnosis of the cause of acute intestinal infarction is accepted as the keystone in surgical care, it is clear that older concepts of this condition are valid. For example, Dunphy's 1936 observation that the importance of abdominal pain of vascular origin is that it is a precursor of acute bowel infarction[20] is correct if this thought is applied to the syndrome of mesenteric arterial thrombosis. Indeed, in this condition the patient may be in hospital being evaluated for abdominal pain and weight loss as the bowel infarcts.[3] This, of course, is not true of the patient with embolization to the superior mesenteric artery.

Similarly, it is in mesenteric artery thrombosis that additive occlusions of celiac axis and/or inferior mesenteric artery are necessary if profound ischemia is to eventuate. Collateral circulation in the mesenteric bed may be profuse and chronic occlusion of two or more vessels may or may not cause acute intestinal ischemia.[6,9]

Results of this trial of revascularization in treatment of acute mesenteric infarction do not provide a definitive answer to the questions raised by this lethal condition. However, of the 38 patients reaching the operating room, only 2 of 21 treated with primary objective of resection survived. In the same time period, in the same hospital setting, 8 of 17 patients survived who were operated upon with a primary objective of producing revascularization before deciding upon resection.

When diagnosis alone is considered, it is unfortunately obvious that neither method succeeded in salvaging a patient with superior mesenteric artery thrombosis. However, in the 6 patients in whom revascularization was attempted, total bowel salvage was achieved in 4. It could be presumed that this method is worthy of further trial.

In patients with superior mesenteric artery embolization, clearly embolectomy prior to bowel resection is the surgical procedure which allows more patient salvage. In this group of 22 patients operated upon, only 2 of 11 were long term survivors of primary resectional therapy while 8 of 11 were long term survivors of embolectomy. Also, in those patients surviving intestinal resections performed without revascularization, intestinal fistulas proved to be lethal. It is clear that if resection is required, revascularization provides sufficient arterial inflow that the bowel anastomoses do heal. One of the 6 patients sustaining an intestinal resection subsequent to bowel revascularization formed an intestinal fistula. In this patient, the aortomesenteric graft occluded some 6-to-8 days following its construction.

Finally, it is reassuring to note that the spectre of superior mesenteric artery shock, well described in the experimental animal, is not characteristically found in human experience.[11] Revascularization of infarcted bowel was achieved in 17 patients, 11 of which had all of the affected bowel re-perfused by systemic blood after periods of mesenteric artery occlusion ranging up to 30 to 48 hours. One patient sustained spontaneously rapidly reversible hyperkalemia.[7] another died of cardiac arrest.[3] The latter did not sustain acute acidosis, endotoxin shock, hyperkalemia, or diffuse intravascular coagulopathy. Rather, this death was more likely an acute cardiac infarction or arrythmia since death occurred quickly after post operative stability of vital functions had been achieved.

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DISCUSSION

DR. GEORGE D. ZUIDEMA (Baltimore): I think that Dr. Bergan and his associates have succeeded in putting together enough cases so that the full spectrum of mesenteric ischemic disease can be displayed, and they are perfectly correct therefore in pointing out in too many instances we have not approached mesenteric arterial occlusive disease as we have arterial disease in the extremities.

They quite properly emphasize the need for very aggressive steps in diagnosis employing diagnostic arteriography and revascularization. The clinical experience reported here in 48 patients emphasizes the tremendous problems which one encounters as a product of delay in diagnosis.

I think that one important ingredient in management of peripheral lesions is the ease of diagnosis and of course this is what is interfering with the management in these particular patients.

One of the problems, of course, in acquiring an accurate diagnosis is the similarity of the presentation of many of these patients with the picture of patients associated with low perfusion or low flow states. I would like to ask Dr. Bergan, although it was not a part of this particular study, in how many patients they have encountered the low perfusion variety which gives us the greater problem in differential diagnosis. I believe that if they could outline the clinical syndrome and the diagnostic steps as clearly for that group as they have for the two groups under consideration, this would be an important service.

I'd also like to ask Dr. Bergan in how many instances they were able to identify a source for the emboli in the embolic group.

I'd like to close with a suggestion that an alternative method of treatment in some of these patients at least is to deal with them clinically by performing a jejunostomy or ileostomy, permitting direct observation of the bowel after the resection has been performed, this permits direct monitoring of the state of the bowel, avoids the need for a second look and provides for later hookup. This has been successful in some recent cases in our hands and is worth considering as an option.

DR. WILEY F. BARKER (Los Angeles): Dr. Bergan and his associates have certainly very nicely categorized the problem of acute vascular lesions of the mesentery and they have done well to try and segregate clearly the diagnoses in terms of the patient's therapy.

Critical in the successful approach to all of these problems is not only the accurate categorical diagnosis, but the accurate early diagnosis. Unfortunately there's no simple non-invasive means which might lead us into an earlier arteriographic proof of the presence of an organic obstruction and the need for operation.

We tend to wait until the clinical diagnosis is unfortunately absolutely clear and this is a treacherous failure.

The ominous prognosis with acute arterial thrombosis underscores the importance that Dr. Dunphy laid on the recognition of chronic abdominal pain of vascular origin a good many years ago.

The recognition by the arteriographer of unusual collateral channels in the meandering mesenteric artery demands good visualization of the origin of all mesenteric branches. As a result, we have found ourselves performing incidental associated mesenteric bypasses with increasing frequency during other intra-abdominal vascular procedures in recent years.

With regard to the results in the face of acute ischemia, it is certainly clear that although few patients survive without revascularization, some do survive with revascularization.

Although there were no survivors in the series in which Dr. Bergan tried to do a revascularization of the arteriosclerotic thromboses, it appeared to me that there were no deaths strictly related to septic vascular suture lines.

Vascular sepsis has been the usual deterrent to most of us in attempting a vascular reconstruction in the face of an abdomen full of potentially dead bowel. Until we can prove that there is a greater risk from the vascular suture line than from enterectomy, we should attempt more reconstructions.

Certainly if there is some other aortic problem such as an aneurysm or advanced atherosclerosis demanding an impossibly major vascular reconstruction at the same time, one might consider the use of the axillary mesenteric bypass that Dr. Sparks and Dr. Imparato have described. That would avoid the presence of a major suture line on the aorta within the abdomen.

Certainly, until we adopt more aggressive attempts at revascularization, we are not going to have many patients salvaged in this terrible catastrophic disease.

DR. JOHN E. CONNOLLY (Irvine, California): I would like to confine my comments to the problem of mesenteric arterial occlusive disease because I think this is much more of a problem than embolic disease. We can get reasonable surgical results in some patients with embolic occlusion but we still have very poor results in the arteriosclerotic occlusive group.

In looking over our results, we have had a similarly high mortality as have the authors, but we do find that over 50% of patients who died with massive gangrene of the bowel have had premonitory symptoms that should have alerted their physicians or surgeons of this diagnosis which would then provide a chance for a prophylactic bypass before the onset of gangrene.

I think it's important to point out that after all of the common causes of abdominal pain have been ruled out, we should consider an aortogram which will identify unsuspected mesenteric arterial disease and give us a chance to revascularize before the onset of gangrene of the bowel.

If we are confronted with a patient with an acute abdomen where we think we are dealing with dead bowel, we feel that it's important to take the patient to the x-ray department on the way to the operating room and get an aortogram. I would like to ask Dr. Bergan if he follows this policy. We believe this information is helping in allowing us to decide whether to revascularize the bowel concomitant with resection.

If the patient does not have occlusive disease anatomically suitable for revascularization, or if the patient's condition does not permit an extensive revascularization concomitant with the bowel resection, one might consider a celiac neurectomy. We have laboratory data that indicate that division of the celiac plexus can prevent borrowing of blood from the mesenteric circulation which may be the critical factor in such patients. As pointed out by Dr. Barker, the patient usually dies because the remaining bowel continues to be ischemic with the development of an anastomotic fistula, peritonitis, and death.

Finally, I'd like to ask Dr. Bergan about the possibility of a prophylactic revascularization in his symptomatic patients which are identified by the enlarged central anastomotic artery that Dr. Barker mentioned.

We have had the opportunity now to prophylactically revascularize the bowel in six patients who were about to undergo reconstructive aortoiliac surgery and were found to have severely compromised mesenteric vessels on the preoperative aortogram. I think that this approach should be helpful in reducing the incidence of gangrene of the bowel.

DR. LESTER F. WILLIAMS, JR. (Boston): I rise primarily to support the suggestion of Dr. Bergan that an aggressive diagnostic approach is needed.

A number of years ago when we first began discussing our interest in extensive bowel disease, we suggested an aggressive approach to these patients as is illustrated on this slide.

Unfortunately, since our interest was primarily the non-occlusive form of mesenteric ischemia, I don't think we stressed the point which Dr. Bergan is making clearly this morning. That is, arteriography, if done early, will help identify those patients with an occlusive phenomenon and thereby identify those patients who need a very early operation.

In addition, often they will differentiate between thrombosis and embolism which is an important technical point.

In addition, I think there's some spin-off from this early aggressive technique. (Slide) This was shown recently during a panel on this subject by Dr. Chris Athanasoulis who was the angiographer who worked with us at Boston City Hospital and is now with Stanley Baum at Mass. General.

He has suggested, on this rather complicated slide, the use of the arteriographic methods including vasodilatation as an important tool of determination of irreversibility in some of the more occlusive states.

In short, I think the arteriographic approach applied early has great potential value.

I would close by asking Dr. Bergan what he thinks is the place of infusion of vasodilators in the patient who has had an embolectomy during the early postoperative period. Would this influence the second look principle?

DR. GEORGE H. A. CLOWES, JR. (Boston): I rise simply to draw attention to the fact that these people present with major postoperative problems. In Dr. Bergan's report, it was apparent that pulmonary failure, cardiac failure, and probably major circulatory failure contributed to the loss of some of his patients postoperatively.

I will not devote time to the pulmonary problem which has been discussed, but rather to emphasize the lethal role of circulatory failure. In a series of some 30 patients treated with glucose potassium insulin who have been in profound septic shock, we have had a remarkable salvage rate of approximately 60%, in terms of converting them to the high output circulatory state typical of patients who recover from severe sepsis. This type of circulatory therapy, whether it is accomplished by GKI, by inotropic drugs or by other methods, such as mechanical support, may make the difference between survival of the whole body, giving opportunity for the bowel itself to heal under adverse circumstances.

Therefore, I believe we must devote a little more attention to this supportive therapy as well as to the technical aspects which have been so nicely brought out by the paper and by the previous discussers.

DR. BROOKE ROBERTS (Philadelphia): Gentlemen, I too would like to congratulate Dr. Bergan and his coworkers on this work. He has emphasized properly the necessity for aggression in treating these patients. One cannot take a passive attitude and wait and see what happens.

I thought it would be of interest to you to mention a couple of patients whom we have seen recently who have gotten into trouble immediately following the aortogram when being studied for intestinal angina. Perhaps there are others of you who have had this experience and will recognize this.

We have had two patients, one in the last week, who was being studied for abdominal pain and had gone through the routine upper GI, et cetera, without positive findings. Finally, an aortogram was done. Both of these individuals had extensive thrombosis of the mesenteric vessels and both of them, patients who had previously merely had pain, were converted into patients who had actual gangrene.

One of these occurred in our own hospital. When we operated the next morning we found necrosis of the bowel and fortunately that fellow is doing well some three years later.

The other was in another hospital and sent to us 48 hours later and this was just last week. He too had necrosis and on that second look had further necrosis; although our graft was working. Whether he will survive remains to be seen.

I think this is a point worth keeping in mind in any patient with chronic obstructive disease of the mesentery, namely, the possibility exists that the aortogram may actually just tip the balance between viability and non-viability.

Both these patients following their study, exhibited more pain, their white counts went up and they became febrile. This sort of change should give you the clue that one should move very rapidly under these circumstances and not wait the 48 hours which we have just seen.

DR. WILLIAM E. DEMUTH, JR. (Hershey, Pennsylvania): About 20 years ago, Dr. Fitts and I worked over the information available at the University of Pennsylvania and found much the same dismal picture that we saw here with mesenteric thrombosis.

It was notable, I think, to notice that in the two surviving patients the white counts were quite low and almost within normal range. I think the name of the game is obvious that you must make an early diagnosis.

I would recommend peritoneal lavage as a possible method by which you might move that patient to the operating room earlier. We don't have big numbers but in four recent experiences it has been helpful in making that determination.

DR. JOHN J. BERGAN (Closing discussion): It's gratifying that so many surgeons have arisen to comment, reflecting an interest in trying to pull through some of these patients.

Dr. Zuidema is correct about the non-organic mesenteric artery occlusion syndrome. It can be identified we believe because of the predominance of cardiac symptomatology. In these patients there is cardiac failure, abdominal pains, GI emptying and leukocytosis.

This is the place for pharmaco-angiography. Installation of appropriate agents will restore bowel viability. One can only repeat the angiography and can watch the leukocytosis which is a very sensitive index of bowel ischemia.

While we've not used the jejunal and ileostomy approach to management of the ends of the bowel. I don't think it would work very well.

In response to the question about pharmaco-angiography or second look; one must decide about the second look at the time of the first operation. There is no way that one can examine the patient or watch the laboratory studies and decide the next day whether a second look is indicated.

In the past we were worried about vascular suture lines becoming infected. Since the outlook in these patients is so poor, it seems logical to us that revascularization was worth a try.

Dr. Connolly's work has been very interesting to those of us interested in bowel ischemia. He has pointed out correctly if one sees the meandering mesenteric artery on a preoperative arteriogram one should look for ischemic bowel in the operating room.

We have not followed his suggestions about revascularizing such cases with aortoiliac disease but one of our colleagues, Dr. Otto Tripple, has had such a patient with bowel infarction after aortoiliac surgery.

Dr. Clowes quite properly has brought to our attention again the superior mesenteric artery shock which has been observed so well in dogs, but I would say that our own very extensive experience with the canine model indicated that none of the findings found in the dog were applicable to man. In fact, man can tolerate mesenteric revascularization quite well.

Dr. Roberts' case may have been thrombosis triggered by the introduction of angiographic contrast media. This is known to occur.

I would be in sympathy with the suggestion made by one of the discussants that patients who have abdominal pain, undiagnosed by conventional means, should have angiography. The patient who looks as though he has cancer but has no cancer, should have an angiogram prior to exploration. In this way, some of these patients can be salvaged early.

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PRECAUTIONS: During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

HOW SUPPLIED: Ampuls, 2 ml, boxes of 10. Multiple Dose Vials, 20 ml. Thera-Ject™ (Disposable Syringes), 2 ml, boxes of 10.

Many things have changed in the operating room in 15 years...

but the Tigan effect hasn't.

(trimethobenzamide HCl)

When Tigan was introduced in 1959, nausea or vomiting was a frequent postoperative occurrence. Advances in surgical technique and anesthetic agents have reduced these incidences. However, when you need control of emesis and need it quickly, Tigan provides the necessary effectiveness with a relative lack of side effects.

Tigan has been used successfully with many different anesthetics and in all types of surgery without potentiating the anesthesia, delaying the awakening or altering the patient's vital signs (although a few instances of hypotension have been reported).

Beecham
laboratories, Bristol, Tennessee 37620

Tigan Injectable is intended for intramuscular administration only: the recommended adult dose—2 ml. (200 mg.) t.i.d. or q.i.d. (It is contraindicated in children)

TIGAN® 200 mg
(trimethobenzamide HCl)
(2ml–200mg)
CAUTION: Federal law prohibits dispensing without prescription.
20ml Multiple Dose Container
Beecham-Massengill
TIGAN®

For prompt control of nausea and vomiting

Tigan® Injectable

(trimethobenzamide HCl)

Please see adjoining page for Brief Summary.

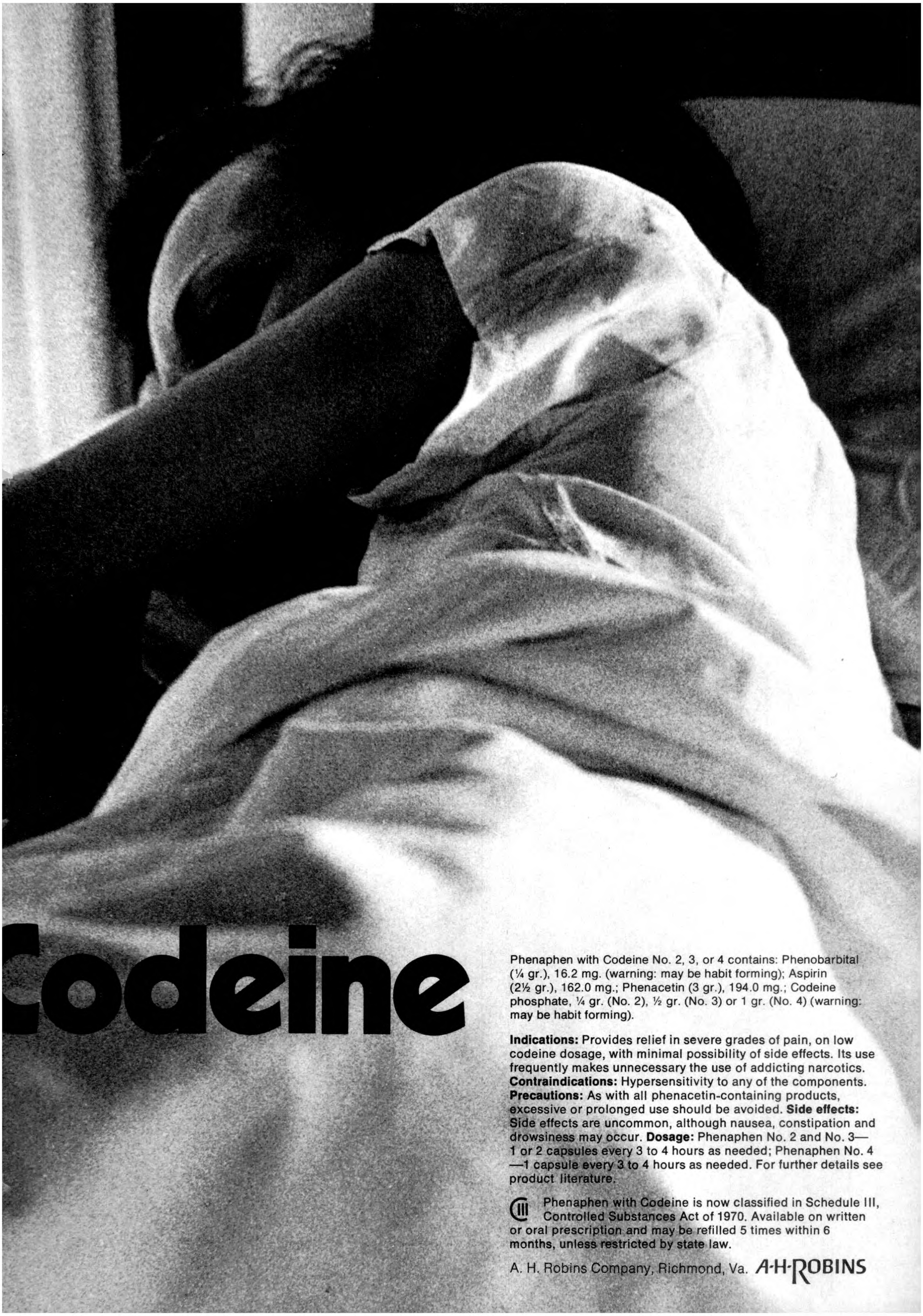
vhen pain goes on...
ınd on...
ınd on–

e analgesic formula that calms instead of caffeinates

Phenaphen® wit

r the patient with a terminal illness, PAIN past, present, and future can dominate thoughts until it becomes almost an obsession. The more he is aware of the pain is now experiencing, the more difficult it is to erase his memory of yesterday's n, and to allay his fearful anticipation of tomorrow's pain.

ely the last thing this patient needs is an analgesic containing caffeine to stimulate senses and heighten pain awareness. A far more logical choice is Phenaphen h Codeine. The sensible formula provides ¼ grain of phenobarbital to take nervous "edge" off, so the rest of the formula can help control the pain more ectively. Don't you agree, Doctor, that psychic distress is an important factor nost of your terminal and long-term convalescent patients?



Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

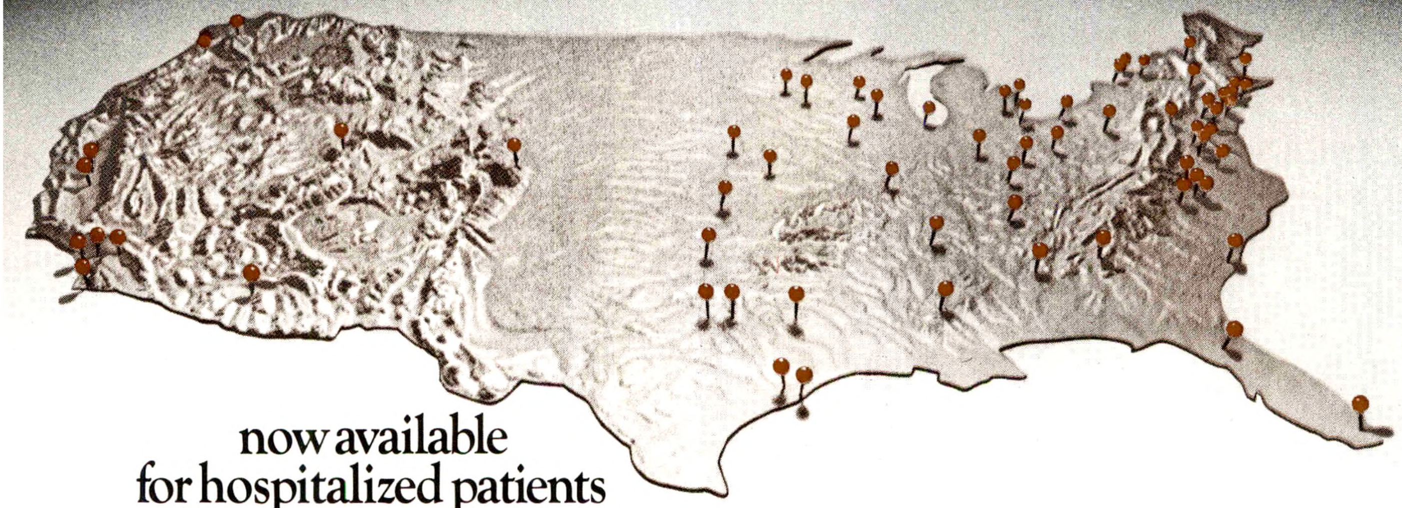
Indications: Provides relief in severe grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

Ⓒ III Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

A. H. Robins Company, Richmond, Va. A·H·ROBINS

An important new antibiotic for serious gram-negative infections*

wide investigational experience already in these areas



now available
for hospitalized patients
in your community

*Due to indicated susceptible organisms.

WARNINGS

Patients treated with Nebcin® (tobramycin sulfate, Lilly) should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, and colistin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

◆ I.M./I.V. Nebcin®
tobramycin sulfate

Lilly
500779

for serious infections including

septicemia

Bacterial cultures should be obtained prior to and during treatment. In patients in whom gram-negative septicemia or neonatal sepsis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box in the prescribing information.

lower-respiratory-tract infections

Nebcin is indicated in bronchopneumonia, pneumonia, empyema, and bronchitis. Most patients treated in clinical trials had one or more of the following underlying respiratory tract conditions: asthma, cor pulmonale, cystic fibrosis, emphysema, bronchiectasis, lung cancer, empyema, and respiratory tract anomaly.

urinary tract infections

Nebcin is indicated in the treatment of serious complicated and recurrent urinary tract infections. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

caused by susceptible strains of

Pseudomonas aeruginosa
Klebsiella-Enterobacter-Serratia group
Escherichia coli
Proteus sp. (indole-positive and indole-negative)
Providencia sp.
Citrobacter sp.
Group D streptococci
Staphylococci,* including
  Staphylococcus aureus (coagulase-positive and coagulase-negative)

*Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Please see following page for summary of prescribing information.

Nebcin® ◆ I.M./I.V.
tobramycin sulfate

Prescribing Information

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, and colistin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., group D streptococci, and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: See WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg./Kg.). The possibility that these phenomena may occur in man should be considered if tobramycin is administered to patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg./Kg./day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg./Kg./day administered in three or four equal doses. This dosage should be reduced to 3 mg./Kg./day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg./Kg./day may be given in two equal doses every twelve hours. The usual duration of treatment is seven to ten days.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg./Kg., subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.[*] To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg./Kg. q. (6 × serum creatinine) h.

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of twenty to sixty minutes.

---

[*] An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function (Dosage at Eight-Hour Intervals)

For Patient Weighing Kg.	Lb.	Usual Dose for Serious Infections 1 mg./Kg. q. 8 h. (Total, 3 mg./Kg./day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg./Kg. q. 8 h. (Total, 5 mg./Kg./day)	
		mg./dose q. 8 h.	**ml./dose**[†]	**mg./dose q. 8 h.**	**ml./dose**[†]
120	264	120 mg.	3 ml.	200 mg.	5 ml.
115	253	115 mg.	2.9 ml.	191 mg.	4.75 ml.
110	242	110 mg.	2.75 ml.	183 mg.	4.5 ml.
105	231	105 mg.	2.6 ml.	175 mg.	4.4 ml.
100	220	100 mg.	2.5 ml.	166 mg.	4.2 ml.
95	209	95 mg.	2.4 ml.	158 mg.	4 ml.
90	198	90 mg.	2.25 ml.	150 mg.	3.75 ml.
85	187	85 mg.	2.1 ml.	141 mg.	3.5 ml.
80	176	80 mg.	2 ml.	133 mg.	3.3 ml.
75	165	75 mg.	1.9 ml.	125 mg.	3.1 ml.
70	154	70 mg.	1.75 ml.	116 mg.	2.9 ml.
65	143	65 mg.	1.6 ml.	108 mg.	2.7 ml.
60	132	60 mg.	1.5 ml.	100 mg.	2.5 ml.
55	121	55 mg.	1.4 ml.	91 mg.	2.25 ml.
50	110	50 mg.	1.25 ml.	83 mg.	2.1 ml.
45	99	45 mg.	1.1 ml.	75 mg.	1.9 ml.
40	88	40 mg.	1 ml.	66 mg.	1.6 ml.

[†] Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules Nebcin® (tobramycin sulfate, Lilly) Injection, 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Ampoules Nebcin, Pediatric, Injection, 20 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Hyporets® (disposable syringes, Lilly) Nebcin Injection, 60 mg. (equivalent to tobramycin) per 1.5 ml., 1.5 ml., and 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., in packages of 24.

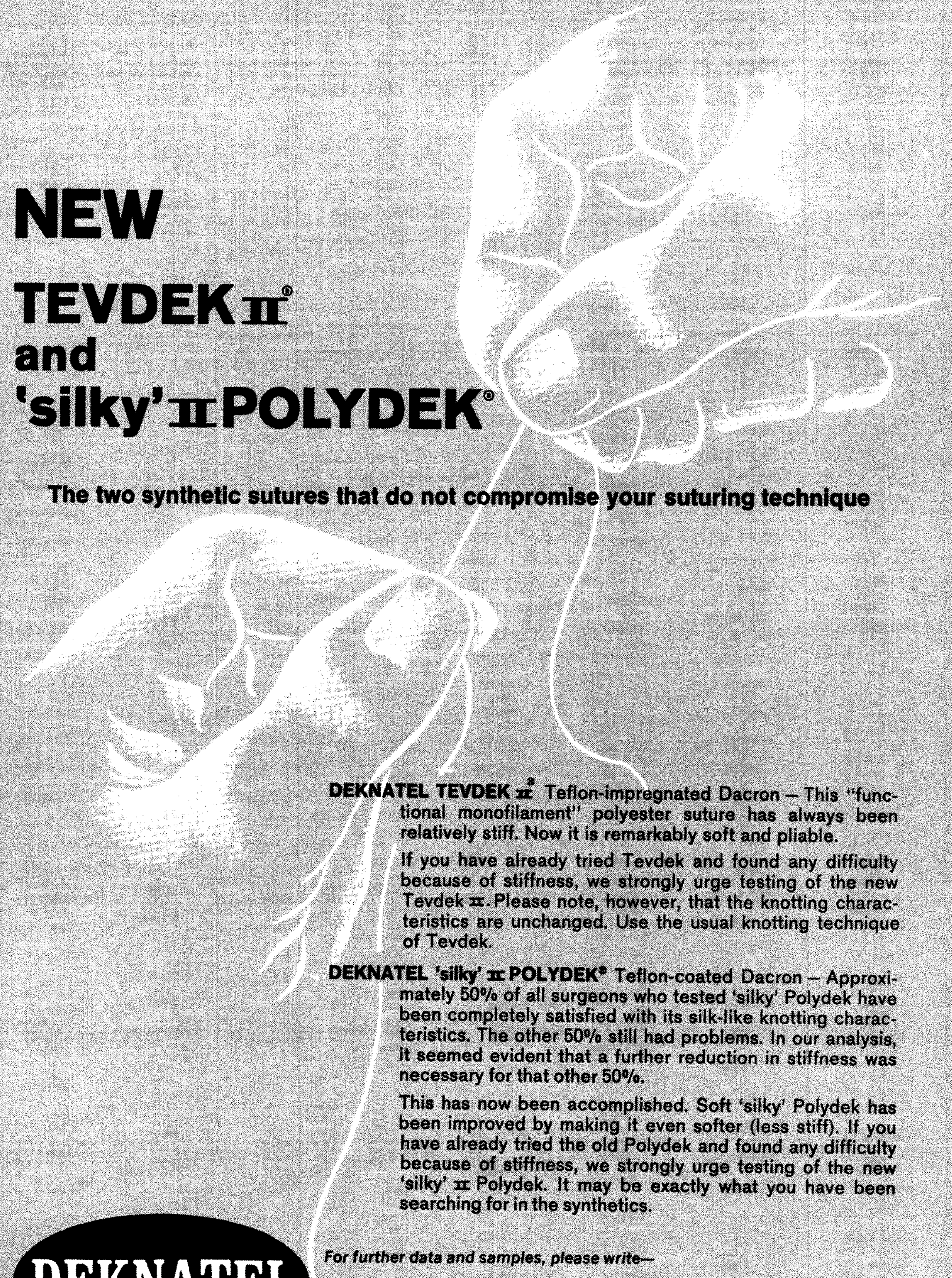
Each ml. also contains 5 mg. phenol as a preservative, 3.2 mg. sodium bisulfite, 0.1 mg. disodium edetate, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [063075]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

500779



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DEKNATEL

For further data and samples, please write—

Queens Village, Long Island, New York 11429

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A SHORT TEXTBOOK OF SURGERY

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Pyridoxine HCl (Vitamin B_6)	5 r
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Warning: Not intended for treatment o pernicious anemia or other primary or secondary anemias. Neurologic invo ment may develop or progress, despit temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

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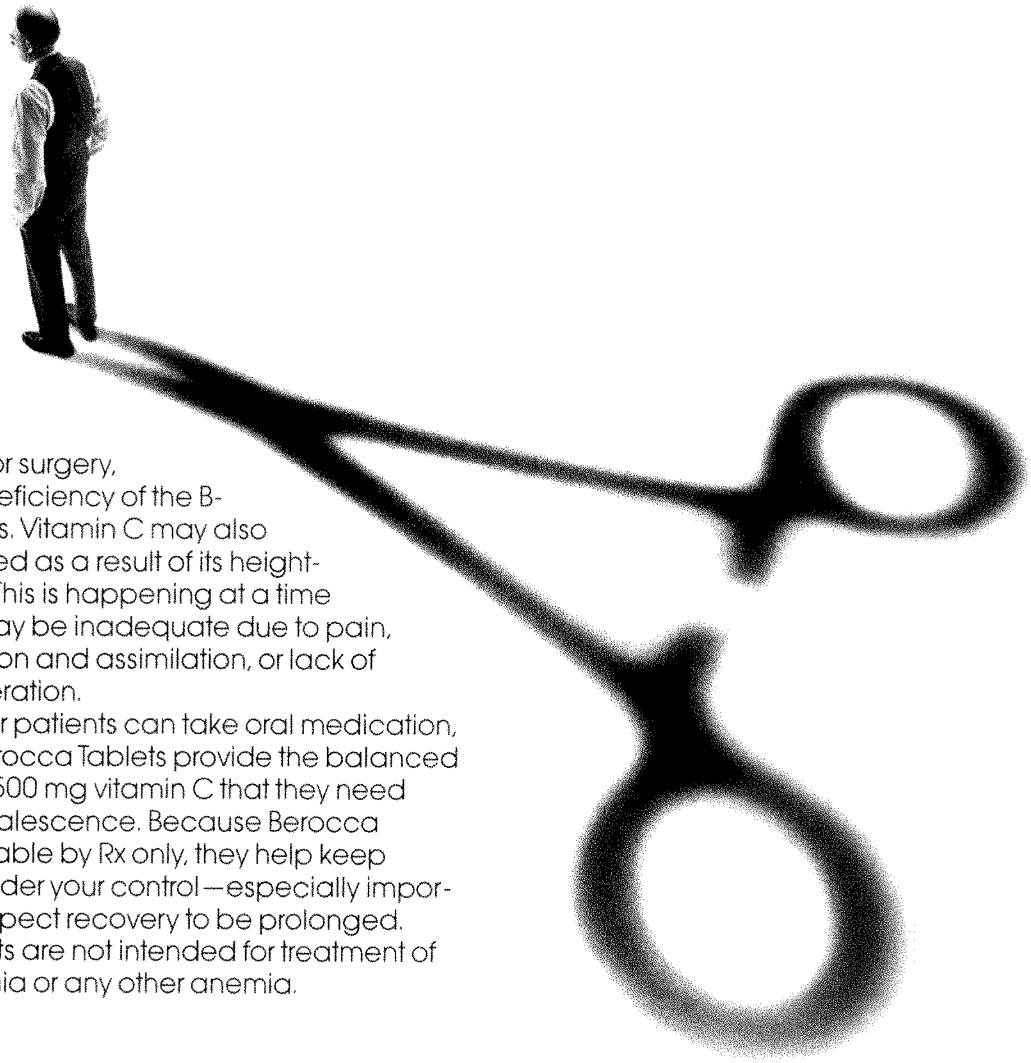
ROCHE

The silent disorder: Vitamin deficiency in the postoperative patient



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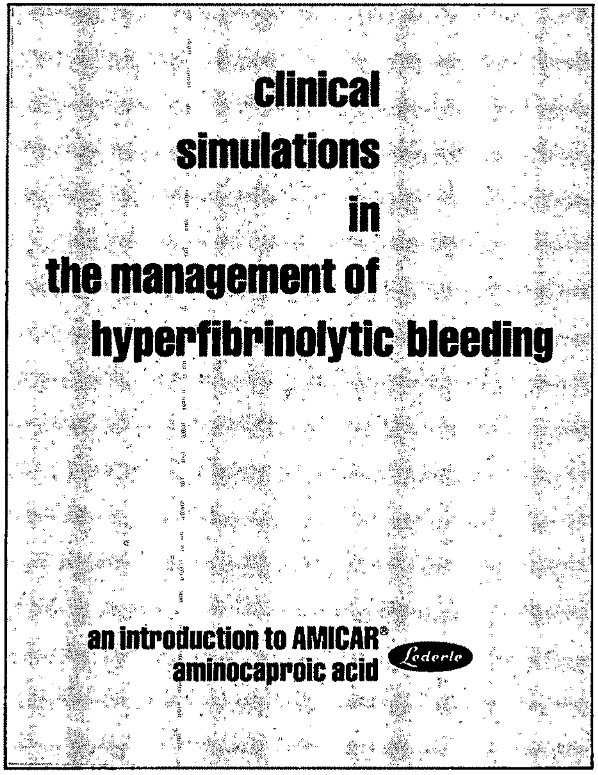
Please see facing page for summary of product information.

A new clinical simulation on the control of life-threatening hyperfibrinolytic hemorrhage



clinical
simulations
in
the management of
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ANS

AMICAR®

AMINOCAPROIC ACID

INTRAVENOUS • TABLETS • SYRUP

INDICATIONS: AMICAR has proved useful, in many instances, in the treatment of excessive bleeding which results from *systemic hyperfibrinolysis* and *urinary fibrinolysis*. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Systemic hyperfibrinolysis, a pathological condition, may frequently be associated with *surgical complications* following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; *hematological disorders* such as aplastic anemia, *abruptio placentae, hepatic cirrhosis, neoplastic disease* such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is *surgical hematuria* (following prostatectomy and nephrectomy) or *non-surgical hematuria* (accompanying polycystic or neoplastic diseases of the genitourinary system).

CONTRAINDICATIONS: AMICAR should not be used when there is evidence of an active intravascular clotting process.

WARNINGS: Safe use of AMICAR has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of child-bearing potential and particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible hazards.

PRECAUTIONS: AMICAR *aminocaproic acid* has a very specific action in that it inhibits both plasminogen activator substances and, to a lesser degree, plasmin activity. The drug should NOT be administered without a definite diagnosis, and/or laboratory findings indicative of hyperfibrinolysis (hyperplasminemia).[1]

[1] Stefanini, M. and Dameshek, W.: The Hemorrhagic Disorders. Ed. 2. New York, Grune and Stratton, pp. 510-514, 1962

The use of AMICAR should be accompanied by tests designed to determine the amount of fibrinolysis present. There are presently available (a) general tests, such as those for the determination of the lysis of a clot of blood or plasma and (b) more specific tests for the study of various phases of fibrinolytic mechanisms. These latter tests include both semiquantitative and quantitative technics for the determination of profibrinolysin, fibrinolysin, and antifibrinolysin.

Animal experiments indicate particular caution should be taken in administering AMICAR to patients with cardiac, hepatic or renal diseases.

Demonstrable animal pathology in some cases have shown endocardial hemorrhages and myocardial fat degeneration. The use of this drug should thus be restricted to patients in whom the benefit hoped for would outweigh the hazard. Physicians are cautioned in the use of this product because of animal data showing rat teratogenicity and kidney concretions.

Rapid intravenous administration of the drug should be avoided since this may induce hypotension, bradycardia and/or arrhythmia.

One case of *cardiac* and *hepatic lesions* observed in man has been reported. The patient received 2 grams of aminocaproic acid every 6 hours for a total dose of 26 grams. Death was due to continued cerebral vascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

If it is accepted that fibrinolysis is a normal process, potentially active at all times to ensure the fluidity of blood, then it must also be accepted that inhibition of fibrinolysis by aminocaproic acid *may* result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of *intravascular clotting* which followed this treatment. Rather, it appears that such intravascular clotting was most likely a result of the fibrinolytic disease being treated.

It has been postulated that *extravascular clots* formed *in vivo* with incorporated aminocaproic acid may not undergo spontaneous lysis as do normal clots. However, it is the consensus of experts that the few reported cases of extravascular clotting could have occurred in the absence of aminocaproic acid treatment.

ADVERSE REACTIONS: Occasionally nausea, cramps, diarrhea, dizziness, tinnitus, malaise, conjunctival suffusion, nasal stuffiness, headache, and skin rash have been reported as results of the administration of aminocaproic acid. Only rarely has it been necessary to discontinue or reduce medication because of one or more of these effects.

Thrombophlebitis, a possibility with all intravenous therapy, should be guarded against by strict attention to the proper insertion of the needle and the fixing of its position.

DOSAGE AND ADMINISTRATION: *INITIAL THERAPY*—An initial priming dose of 5 grams of AMICAR administered either orally or intravenously followed by 1 to 1¼ gram doses at hourly intervals thereafter should achieve and sustain plasma levels of 0.130 mg./ml. of the drug. This is the concentration apparently necessary for the inhibition of systemic hyperfibrinolysis. Administration of more than 30 grams in any 24-hour period is not recommended.

INTRAVENOUS: AMICAR *aminocaproic acid* Intravenous is administered by infusion, utilizing the usual compatible intravenous vehicles (e.g. Sterile Water for Injection, physiologic saline, 5% dextrose or Ringer's Solution). RAPID INJECTION OF AMICAR INTRAVENOUS UNDILUTED INTO A VEIN IS NOT RECOMMENDED.

For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 16 to 20 cc. (4 to 5 grams) of AMICAR Intravenous be administered by infusion during the first hour of treatment, followed by a continuing infusion at the rate of 4 cc. (1.0 gram) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

ORAL THERAPY: If the patient is able to take medication by mouth, an identical dosage regimen may be followed by administering AMICAR Tablets or 25% Syrup as follows: For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 10 tablets (5 grams) or 4 teaspoonfuls of syrup (5 grams) of AMICAR be administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 gram) or 1 teaspoonful of syrup (1¼ grams) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

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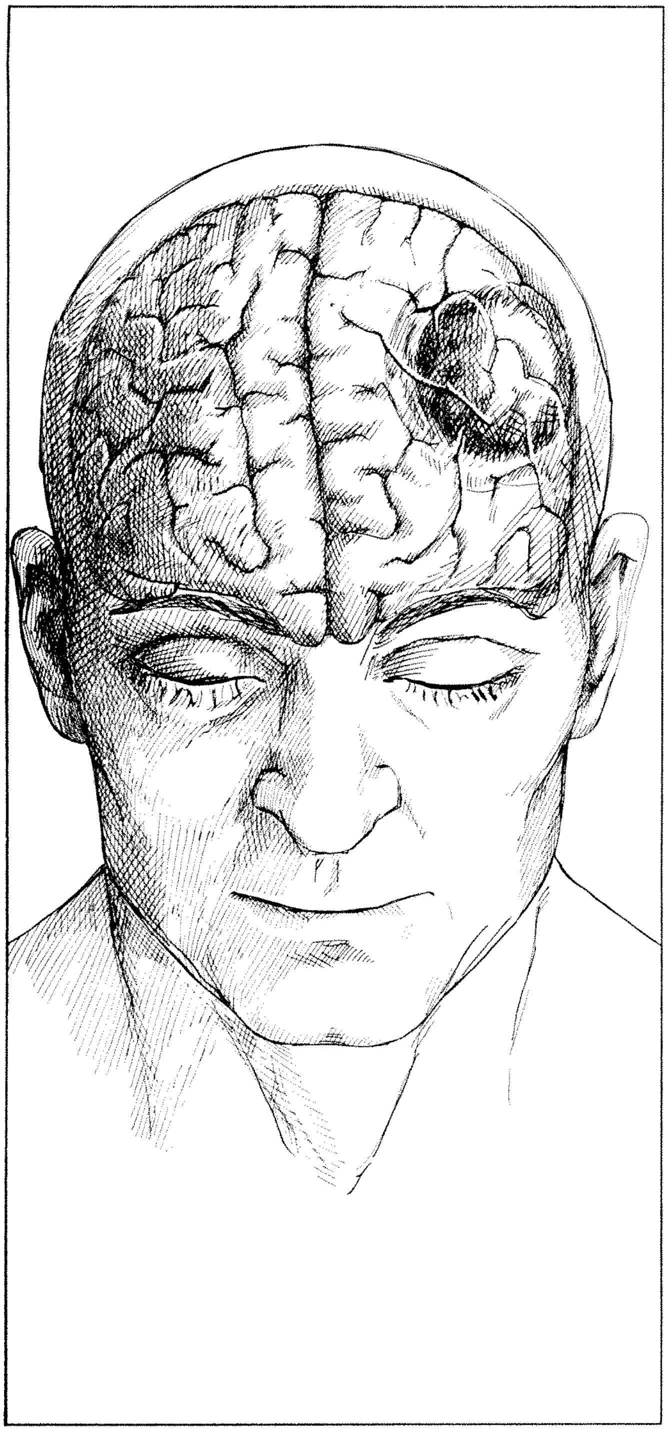
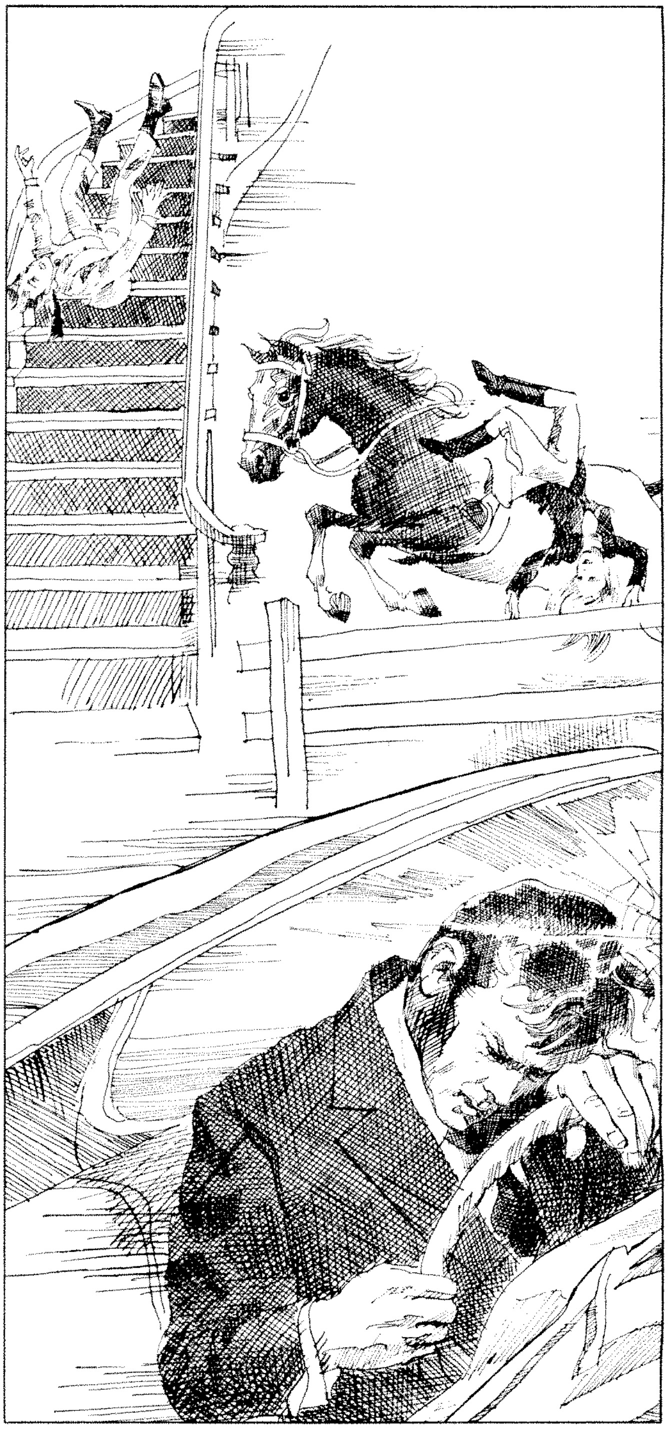
cerebral

expect it as a possible complication of primary or metastatic brain tumor.

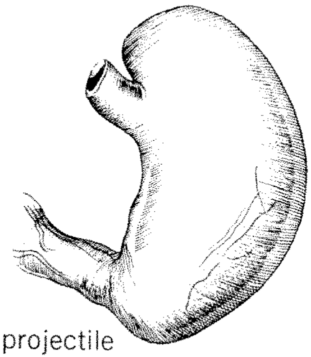


expect it in the presence of severe head injury.

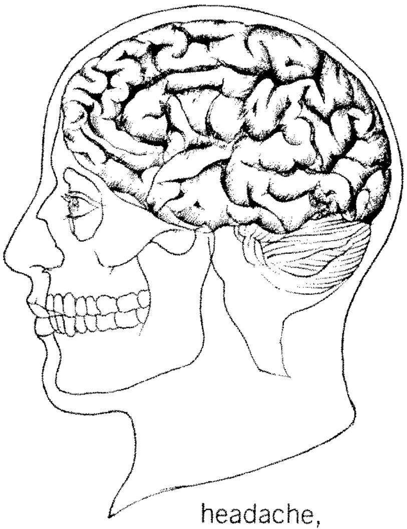


edema*

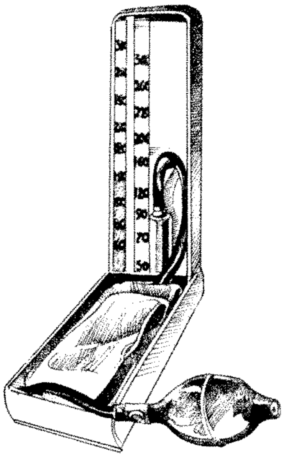
suspect it in the presence
of signs and symptoms such as these:



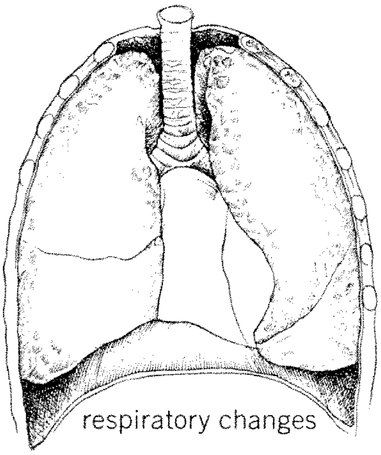
projectile
vomiting



headache,
altered consciousness

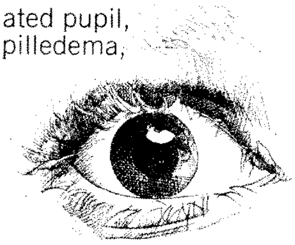


increased
blood
pressure

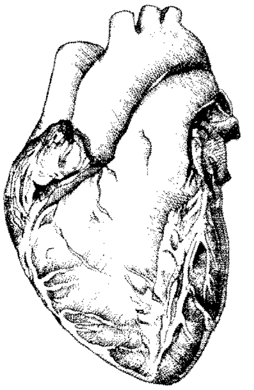


respiratory changes

dilated pupil,
papilledema,



unilateral or bilateral
abducens palsy



bradycardia

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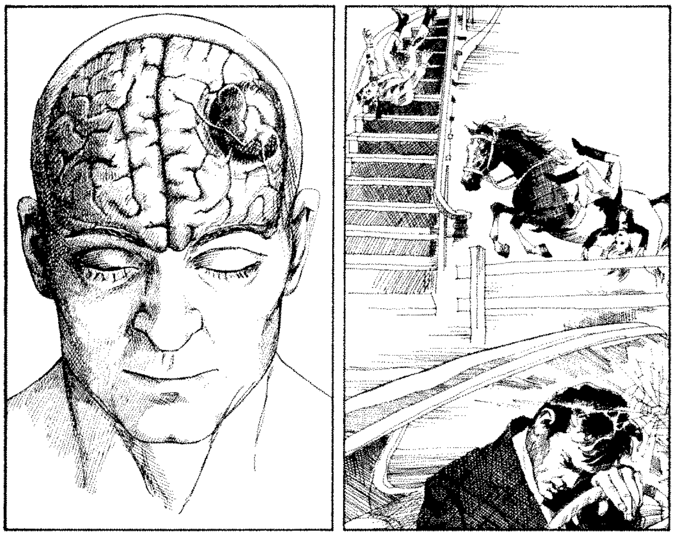

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Ritchie WP: The emergency care of cerebral injuries, J Lancet *86*:255, June 1966.

The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

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Injection DECADRON Phosphate is generally administered initially in a dosage of 10 mg dexamethasone phosphate (2.5 ml) IV followed by 4 mg dexamethasone phosphate (1 ml) IM every six hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For the palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy should be individualized with either Injection DECADRON Phosphate or Tablets DECADRON (supplied as 1.5-, 0.75-, 0.5-, and 0.25-mg tablets). Two mg two or three times daily may be effective. The smallest dosage necessary to control cerebral edema should be utilized. The usual precautions in regard to corticosteroid therapy should be employed, and antacids, anticholinergic drugs, and diet measures to prevent gastrointestinal ulcer or hemorrhage should be considered. Please read the brief summary below, and consult full prescribing information before prescribing or administering.

Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

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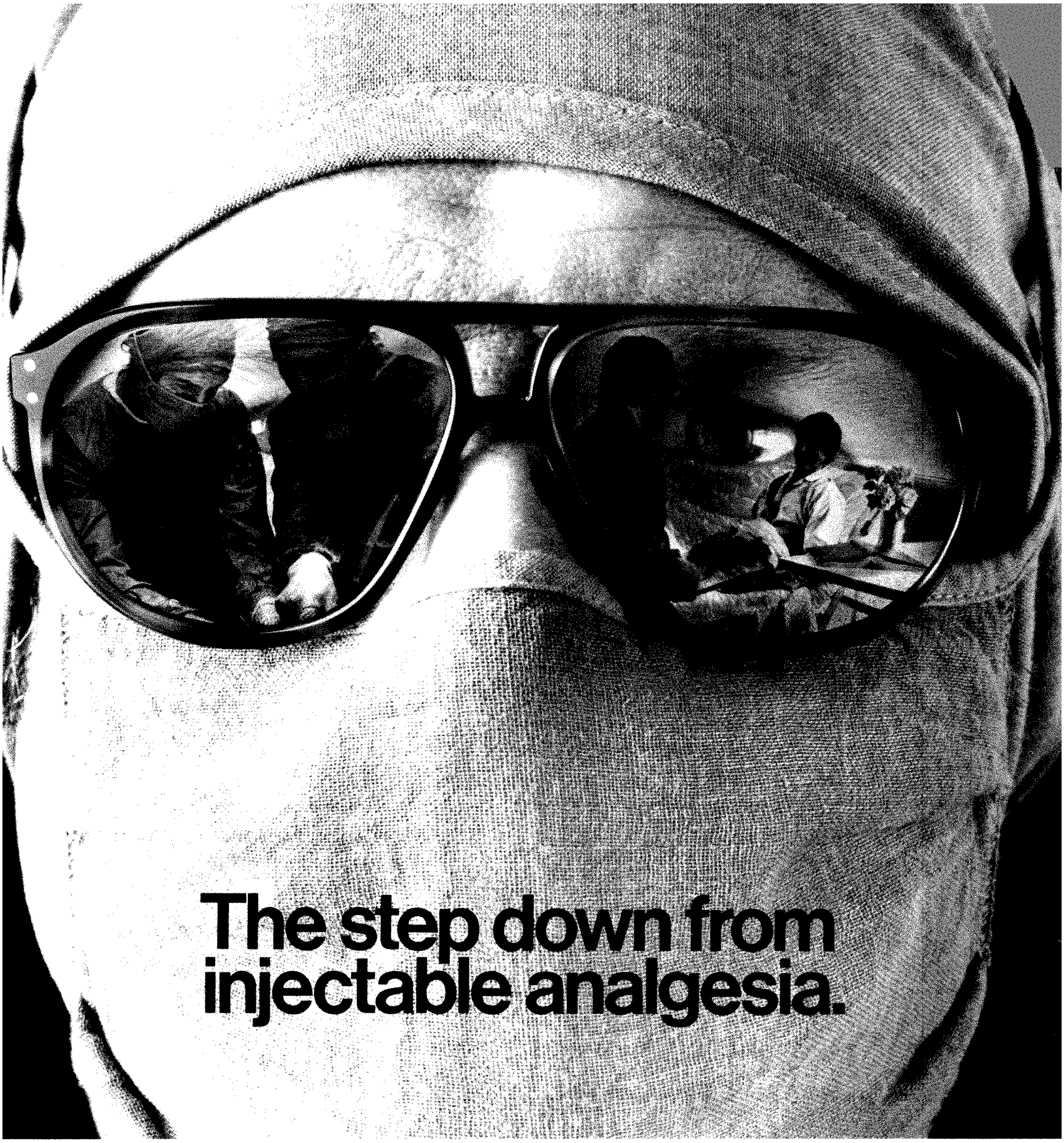
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See facing page for Brief Summary

*See dosage and administration section of Brief Summary

[illegible]

Whenever an APC/narcotic is indicated.

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Percodan® Tablets ©II

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS: *Drug Dependence:* Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Percodan, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, Percodan is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical oourse of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Serious overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of Percodan may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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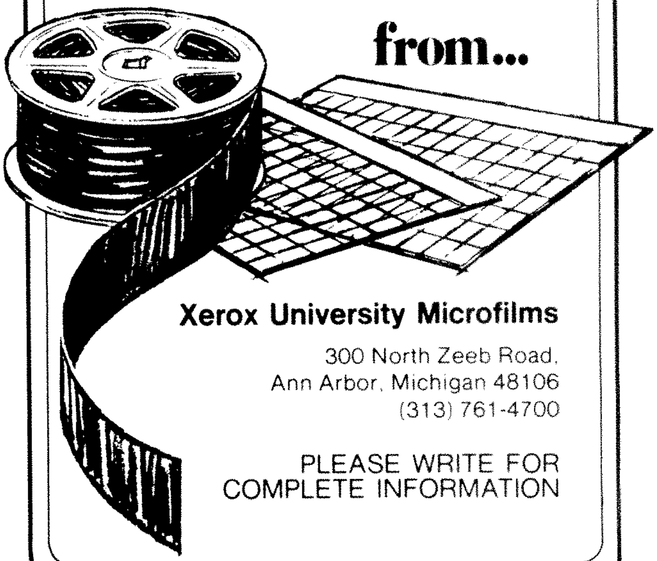

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Ischemic Colitis:

An Useful Clinical Diagnosis, But is it Ischemic?

LESTER F. WILLIAMS, JR., M.D.,* JACK WITTENBERG, M.D.†

From the Division of Surgery,
Boston City Hospital and Boston
University Medical Center

ISCHEMIC COLITIS or, more correctly, vascular disease of the colon has been known for close to 100 years. Early concern equated this condition to colonic infarction secondary to accidental arterial ligation during surgical procedures. During the 1950's colonic infarction occurring after inferior mesenteric artery ligation during colonic surgery for carcinoma or aortic surgery was the primary interest. Although it was known that an occasional patient manifested a relatively benign process after such arterial ligation, it was not until 1963 when Boley and associates[4] reported 5 patients with a disease they labeled "reversible vascular occlusion of the colon" that emphasis upon the milder component of this problem was provided. In 1966 Marston et al,[27] reported on 16 patients who manifested three stages of a spontaneous disease which they labeled ischemic colitis.[28] Since that time there has been an ever increasing interest in the problem of spontaneously occurring ischemic colitis. However most reports have stressed specific components of the disease, i.e. a new diagnostic point[10,16] or a select group of patients.[17,19,22,33,35] This review is based upon our experience with 55 cases of ischemic colitis that span the currently recognized spectrum of this lesion.

Material

Patients included in this review fulfilled rigid criteria which were deliberately developed to prevent overlap between ischemic colitis and other types of colonic abnormality. It is realized that such rigid selection might have excluded some patients with the lesion, but this was felt to be less important than the problem of significant overlap. Our data include only acute colonic disease occuring in a patient with the following characteristics: 1) over the age of 50 and without similar or subsequent episodes, 2) without evidence of ischemic disease elsewhere within the gastrointestinal tract, 3) not being treated with antibiotics, 4) without evidence of an enteric infection, 5) proctoscopic examination, when positive, indicates an acute mucosal inflammatory disease, 6) radiologic abnormalities, if present, indicate an acute colonic ulcerative or exudative process[42] which in surviving non-operated patients undergoes evolution to healing or stricture and 7) available histologic specimens demonstrating mucosal and/or submucosal destruction, edema or hemorrhage. We recognized that neither the histologic evaluation, nor the barium changes by themselves are specific for this lesion but the criteria used are those which we[40,42,43] and others[4,5,7,22,26,27] have considered as diagnostic of ischemic colitis.

As indicated in Table 1, the 55 patients represent 46 with spontaneously occurring ischemic colitis, four with ischemic colitis occurring early after inferior mesenteric artery ligation, one with ischemic colitis occurring as a complication of a colonic obstruction secondary to carcinoma of the sigmoid and 4 occurring late after an abdomino-perineal resection. Analysis of the clinical features is similar whether or not the groups are analyzed as

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Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

*Professor of Surgery, Boston University School of Medicine; Director of Surgical Services, Boston City Hospital.

†Assistant Professor of Radiology, Harvard Medical School; Associate Radiologist, Massachusetts General Hospital.

Reprint requests: Lester F. Williams, Jr., M.D., University Hospital, 75 East Newton Street, Boston, Mass. 02118.

TABLE 1. *Ischemic Colitis*

Patients	Etiology
46	Spontaneous
4	Early after IMA ligation
1	With colonic obstruction
4	Late after abdomino-perineal resection

46 spontaneous cases, as 50 cases including the 46 spontaneous ones plus those occuring late after an abdomino-perineal resection or as an entire group of 55 patients. For example the 46 patients with spontaneous disease were comprised of 23 men and 23 women with an average age of 70.6 years (range 55 to 90 years). Pain was present in 75%, diarrhea was the prominent feature in 61% and when present the diarrhea was bloody in 69%. Of this group 41% were operated upon with a survival rate of 58%. In the 59% that were not operated upon the survival rate was 63% so that the overall survival was 61%. When all 55 patients are considered, there were 29 men and 26 women whose average age was 70.1 years—(the range 50-90 years). Pain occurred in 76%, diarrhea in 62% with 76% of these patients having grossly bloody diarrhea. Forty-two per cent were operated upon with a survival rate of 61% whereas in the non-operated group, a survival rate of 63% was observed. Our data on radiologic evaluation, endoscopic observations and histologic study do not vary from our previous reports.[40,42] The location of the process for the 46 spontaneous cases is shown in Fig. 1. The endoscopic and/or barium studies always documented the full length of the colonic involvement at the time of the first study. In the patient with ischemic colitis secondary to colonic obstruction the barium enema done after the transverse colostomy was established revealed that the ischemia process spared several centimeters of bowel proximal to the carcinoma. A similar tendency to spare the distal several centimeters of colon was observed in the patients with ischemic colitis occurring late after abdominoperineal resection.[43]

On the basis of clinical manifestations we could separate our patients into two distinct groups, those with severe disease and those with mild disease. The prognosis and the therapy varied for such subgroups. The severe group includes those patients with significant peritonitis, either localized or generalized, as well as those patients whose ischemic process was not resolving within 2 to 3 weeks. Others have characterized such patients as having fulminant, gangrenous or necrotizing colitis[17,26,35] or persistent ischemic colitis.[7] The mild group includes: 1) those without significant peritonitis whose clinical manifestations of ischemia have resolved in two weeks, and 2) those with stricture. Such patients have been labeled as transient[4,7,26,27] or stricture cases.[26,27] Using this clinical background, 13 of our patients with spontaneous disease had a severe course. This 28% of the patient population included 8 (44%) of the deaths, and accounted for 10 (53%) of the operations. In this group of 13 patients with severe disease, we observed that 12 had ischemic colitis as their primary problem and only one had ischemic colitis incidental to a more severe generalized problem. Within those 12 patients with primary severe ischemic colitis there were 7 deaths. In contrast, the 33 patients classified as having mild disease accounted for 10 deaths and 9 operations. Of the 10 deaths, 8 were attributed to causes other than the ischemic colitis because they occurred in patients in whom the ischemic colitis was an incidental part of some other severe generalized disease process.

The patient with ischemic colitis secondary to colonic obstruction and all 4 with the lesion occurring late after an abdominoperineal resection had mild disease and all survived. Three of those with ischemic colitis after inferior mesenteric artery ligation had severe disease and all died, whereas, the one with mild disease lived.

Using our current knowledge of the disease process, its

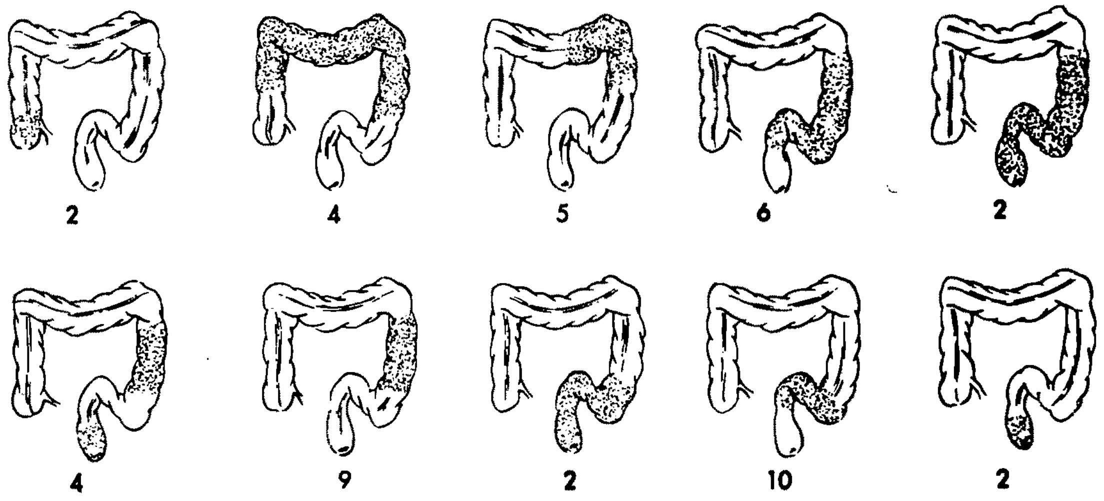

FIG. 1. Distribution of the lesion in the 46 patients with spontaneous disease.

clinical manifestations and proper surgical therapy, we retrospectively evaluated the appropriateness of surgical intervention. In the 46 patients with spontaneous disease, 11 operations (58%) were necessary and appropriate. Seven operations done for stricture or possible colonic carcinoma would not now be performed. One operation was questionable since it was done in the presence of equivocal peritonitis to exclude the presence of gangrenous bowel which was not found. Thus, 37% of the operations performed in our group of 46 patients with spontaneous ischemic colitis could be avoided. Equally important, three patients who were not operated upon clearly had clinical evidence of peritonitis that today would be considered a basis for prompt operative intervention. Thus 11% of the group treated without surgery should have been operated upon. If one considers the entire group using the same criteria, necessary operations were done in 15 patients, (63% of the operations) unnecessary in 8 (33%) and questionable in one (4%). There were an additional 5 patients who should have been operated upon but were not. If the groups are considered according to the severity of their disease, the severe group, which includes 8 deaths and ten operations, contains 3 patients who died in spite of an appropriate operation, 2 patients who died without operations but who clearly needed them, one death in a patient with a questionable operation and one death in a patient whose operation was inappropriate. Of the 33 patients with mild disease, 7 of the 9 operations would now be judged to be unnecessary.

TABLE 2. *Acute Ischemic Bowel Disease*

	Segmental Ischemic Colitis	Extensive Bowel Ischemia
Clinical	Diarrhea often bloody	Severe diffuse abdominal pain
	Mild lower abdominal pain	Cardiac abnormalities
	Normotensive	Shock and electrolyte imbalance
Etiology	IMA	SMA
	No occlusion 95%	No occlusion 50%
	Occlusion 5%	Occlusion 50%
Prognosis	Fair to Excellent	Dismal

Discussion

Useful clinical entity: A review of the clinical material presented in our series when coupled with that available from other reviews[2,7,9,20,26,27,38] supports our conclusion that ischemic colitis has become a well recognized clinical entity. Although neither the histologic material nor the barium studies are specific by themselves, the total clinical picture is now considered specific.[2,7,9,26,27,38,40] The designation ischemic colitis not only separates this problem from other recognized diseases, especially ulcerative colitis and granulomatous colitis, but also provides both therapeutic and prognostic implications which differ from other colonic processes.

In summary ischemic colitis is an acute colonic process occurring in either males or females of an average age of 70 years. The primary complaint is mild abdominal pain associated with significant diarrhea which is commonly bloody. The disease is diagnosed by observing an acute ulcerative process in the mucosa on barium and/or endoscopic studies, or an exudative process[42] manifest on barium studies as thumbprinting with the associated secondary characteristics of transverse ridging, spasm, or rigidity and on endoscopic examination as hemorrhagic bullae. Histologic evaluation, whether available from endoscopic material or surgical material shows the presence of an acute mucosal process with extensive submucosal edema and/or hemorrhage. There may be an inflamatory component, but a specific type of organism is not essential for diagnosis since the absence of bacterial colonization is not uncommon. The extent of the process is determined by the first examination since progression to other segments of bowel is quite unusual. This observation has not been commented upon before. The lesion is differentiated from other processes that might present with similar manifestations by its rapid change often with observable change in the barium studies and/or the endoscopy findings within 5 to 7 days. Progression to healing or to mild stricture is anticipated in the majority of patients. The location of the lesion has usually been fixed as "around the splenic flexure." However, on the basis of reviews which include over 300 patients[7,26,38] the right colon was involved in 8%, the rectum and rectosigmoid in 5%, the transverse colon (with or without involvement of either flexure) in 14%, and the left colon in 73%. Variations noted in previous reviews which have stressed different locations can probably be explained on the basis of patient selection. For example, Thomas[38] showed that 73% had involvement in the area of the splenic flexure. However, he depended almost exclusively upon barium studies for selection of his patients thereby excluding the majority of patients with the more distal lesions. Marcuson[26] noted a 23% incidence of isolated splenic flexure involvement. However in this review very few severe cases are included, thus this group is heavily weighted by patients with very mild disease.

In our experience patients suffering from ischemic colitis, a segmental ischemic process, can be differentiated from those with acute extensive bowel ischemia.[41] Table 2 outlines the principal differences as we have reported before.[42] The differentiation is possible in spite of the fact that patients with extensive bowel ischemia commonly have colonic involvement. Such a separation of patients into groups with extensive or segmental bowel ischemia provides for different diagnostic and therapeutic guidelines.[41,42]

If ischemic colitis is to be a useful clinical entity then the disease process must not only be characterized on a clinical basis, as has been done above, but one must also be able to provide useful therapeutic and prognostic information. In their article which popularized the term ischemic colitis, Marston et al.[27] suggested three stages: gangrenous, transient and stricture. Since that time many variations or subdivisions have been suggested. Stress has been placed upon a gangrenous, fulminant or necrotizing process,[17,20,29,35] the bacterial component,[26] colonic ischemia with occlusion of the mesenteric arteries,[14,19,24,29,33,46] ischemic proctitis[14,22] or the transient case[4,5,7,26,38,42] with[2,7,9,21,24,26,38] or without stricture. Still others have stressed the association of ischemic colitis with a more generalized disease process[17,20] with colonic obstruction before[8,37,38] or after[9] a colostomy, with a young age[11,13,31] or with the use of contraceptive medications.[12,15,18,23,39] Based upon our experience and our review of the literature, we now feel that little is gained from separating ischemic colitis into other than two categories, severe and mild. The classification is thus based upon clinical manifestations and not upon presumed etiology, special population characteristic or specific process such as stricture.

Some of the variations noted in the literature on ischemic colitis are clearly related to populations being evaluated. For example cases of a severe nature may have been included or excluded. Our data include a 29% incidence of severe cases and Boley's,[7] a 28% incidence; yet Marcuson[26] in his review of 122 cases has but a 12.5% incidence of severe lesions. Further confusion can occur because severe cases of ischemic colitis do occur as a part of some other severe generalized disease,[17,20] but in many instances patients who have both an extensive disease process and bowel ischemia have extensive acute bowel ischemia, with spread of the process into the colon especially the right colon.[41]

Severe cases of ischemic colitis clearly include those with gangrene or a fulminant course as with necrotizing colitis, or clostridal colitis[26] and the cases of colonic infarction secondary to inferior mesenteric artery ligation. There are, however, additional severe cases where the fulminant nature is not obvious within hours[17,21] but develops as the disease progresses over several days. Finally the severe group should include those patients whose process is prolonged without resolution beyond two weeks. Although we have observed a patient who required 5 units of blood and several who needed one or two units of blood transfusion, to date no patient has been recorded who needed emergency resection for control of bleeding due to ischemic colitis. Severe defined in this manner assumes therapeutic importance because all of these patients will require resection. The only real issue is timing. It is clear that proximal decompression and diversion are not appropriate because there are in our own experience, as well as in the literature, a number of cases in which the ischemic process continued in spite of these procedures.

From our own data as well as that in the literature it is obvious that the patients with the most fulminant kind of disease[17,20,21,29,35] may have generalized peritonitis shortly after the onset and/or may have massive colonic distension which is not dissimilar to that seen with toxic megacolon.[2,21,35] These patients should have an emergency operation. The difficulty, as pointed out by a number of authors[17,35,37] is that resection may not be undertaken because the serosal reflection of the ischemia is equivocal, especially when pulsatile vessels are documented either by angiography or, as more commonly, at the operative table. With these findings the possibility of colonic ischemia is dismissed. Although the majority of reports show a high death rate (4 of 5,[35] 7 of 12 in our own experience) there are reports of survivors in 5 of 7 when aggressive resection is undertaken.[17] The patient who has a relatively mild process at the onset but progresses over the course of a few days to a more fulminant disease[7,40] also requires immediate resection. This decision is based upon clinical evaluation for peritonitis, localized or generalized. The last category of the severe ischemic colitis is the patient with persistent disease.[7,40] Although this is more difficult to define, most have agreed that active disease extending beyond two weeks, especially if bloody diarrhea continues, provides a poor prognosis. An exudative process, as documented on barium enema[42] is likewise a poor prognostic sign. It should be noted that stricture has not been included as a criterion of severity and thereby is not included as a specific indication for operation. This will be discussed subsequently.

Patients with ischemic colitis of the mild variety include those usually labeled as transient[4,5,7,26,27,38,40,42] and the majority of those labelled as stricture.[2,7,9,21,24,26,38,40,42,43] Mild ischemic colitis is the type most commonly seen with colonic obstruction.[8,9,17,37,38] As will be discussed in detail later, the mild form can occur after occlusion of the inferior mesenteric artery.[19] Mild ischemic colitis can occur in the course of some other significant generalized disease. While it may contribute to the overall problem, seldom is such mild ischemic colitis the direct cause of death. This was true in 8 of our 10 deaths in the 33 patients with mild disease. The diagnosis of mild ischemic colitis depends upon the absence of the specific features of severe disease as outlined above.

The most critical features for the diagnosis of mild ischemia are related to the previously described changes on barium study and/or endoscopy especially when coupled with a rapid change over a relatively short time.[7,26,38,42] Our review stresses several important observations for patients in this category: 1) In contrast to our initial suggestion[40] arteriography is not essential to clinical management. 2) When this lesion occurs in association with colonic obstruction, one must recognize that the ischemic colitis is often the most prominent part of the clinical picture and thus could lead to an oversight relative to the precipitating carcinoma, a potentially disasterous result. Of equal importance to the surgeon is the observation that if this lesion occurs after a transverse colostomy[9] or a colonic resection,[9] the mild ischemic colitis can be overlooked or attributed to "disuse atrophy." In these cases the partial obstruction associated with the ischemic colitis can interfere with surgical results from resection and/or closure of the colostomy.

Our inclusion of most cases of ischemic stricture in the mild category of disease requires justification for two reasons: 1) to date most authors have insisted upon separating stricture from other forms, 2) stricture has almost uniformly been an indication for surgical resection. We challenge both the diagnostic and therapeutic implications of such a designation. This separation is based upon the two observations that stricture was neither gangrene nor transient and yet stricture required an elective resection. That severe fibrotic stricture of the colon can occur secondary to ischemic colitis and can lead to a functionally significant colonic obstruction is established.[10,14,21,24,27,33] However as we reviewed the published data we were impressed that only 7 cases[10,14,21,24,27] clearly document a functionally significant colonic obstruction. It must be acknowledged that many reports do not contain sufficient data to be certain as to the degree of obstruction. Nevertheless there are reports in which the stricture was clearly not associated with significant obstruction.[2,9,12,13,14] We[43] and others[2,38] had observed ischemic strictures that remained stable and remained without obstructive symptoms. Finally in a previous report[42] we have stressed the many secondary features of ischemic colitis that interfer with distensibility and/or motility of the colon. If these features are the basis for the diagnosis of stricture, then its prevalence has been over stated. In summary we have not used a separate category for ischemic stricture for the following reasons: 1) the incidence of fibrotic stricture *with* functionally significant colonic obstruction while undetermined to date is probably very low, 2) if the patient's clinical course is mild, as has been true for most recorded strictures, observation over the time required to establish that colonic obstruction is present is safe, 3) if the patient's clinical course is severe, either by virtue of a progressive or a prolonged process, then resection is appropriate on the basis of severe disease.

The issue of ischemic stricture has been compounded because most reviews include patients whose stricture was resected because of a preoperative diagnosis of colonic carcinoma. It is not always clear whether ischemic colitis has been resected because of a stricture with partial obstruction or because carcinoma was suspected. The evolution of the ischemic process as reflected in barium studies is now clear enough so that confusion with carcinoma should not occur. If doubt exists, colonoscopy should be able to settle the issue.[16,45]

The suggested classification of ischemic colitis into severe or mild not only excludes specific processes such as stricture but it also excludes groups designated by etiology or population characteristic. One area of major concern with respect to the problem of ischemic colitis relates to its occurrence in patients younger than the age of 50. The possibility that in these younger patients, venous occlusion, particularly in association with use of contraceptive medications, is a significant etiology is also of concern. We excluded patients below the age of 50 in order not to confuse the process with the other diseases such as ulcerative colitis and granulomatous colitis. We feel that this excluded some patients with ischemic colitis and indeed we have seen two patients at a younger age, who by all other criteria would have been labeled as having ischemic colitis. The available reports on mesenteric ischemia and the use of contraceptive medications contain 12 patients in whom colonic involvement has been the only bowel involvement.[11-13,15,18,23,25,31,32,39] In these 12 patients, one has had an angiogram and two have had resection. Since Polk has established the criteria for venous occlusive disease as documented by angiography,[34] it seems reasonable to conclude that the normal angiogram means that the one patient so far reported did not have any of the criteria of venous occlusive disease. By the same token the pathologic specimens for the two patients with resection do not support venous occlusion as a cause because it has been amply documented that histologic changes induced by either arterial or venous occlusive disease are similar.[25,26,28] Although the rate of progression of the lesion may vary, histologic criteria for differentiation of arterial from venous occlusion are not secure. We therefore conclude that, in spite of suggestions to the contrary, there is no objective evidence available at the present time to support the concept that ischemic colitis occurring in young patients taking contraceptive medication is due to venous occlusion. Further circumstantial evidence for this conclusion is the fact that the literature contains 20 cases of ischemic colitis occurring in patients under the age of 50, none of whom had been taking contraceptive medications.[4,11,13,31] From the available clinical material these patients are, by all criteria other than age, similar to the patients reported as having spontaneous ischemic colitis[7,26,38,42] in this series. Therefore we conclude that ischemic colitis as generally defined does occur in patients under the age of 50 but it is rare.

In an earlier report,[40] we suggested that ischemic colitis occurring as a result of occlusion of the inferior mesentery artery might be a more severe form and therefore might need resection as routine therapy. Our recent experience as well as that provided by other reports does not substantiate that guess. Colonic infarction after surgical procedures that include ligation of the inferior mesenteric artery or its branches is well established.[19,33,43,45,46] What is more significant from the point of view of ischemic colitis as an entity, however, is that in a review of the literature on colonic ischemia after aortic surgery, Johnson and Nabseth[19] found only 99 cases (1.5%) in over 6000 operations. Of these 99 patients with colonic ischemia occurring after inferior mesenteric artery ligation, 26% had mucosal involvement only and 18% had stricture. Thus, although 56% did in fact have the traditional infarction of the colon, an almost equal number manifest more superficial lesions. The therapeutic implications for this type of ischemic colitis do not differ from those presented earlier in this article. However one must remember that only 29% of spontaneous ischemic colitis patients are apt to have severe disease, whereas, 50 to 60% of patients with ischemic colitis after arterial ligation may have severe disease. In this special group the early clinical observations may not always predict the eventual severity of the disease,[33] because the clinical basis for the diagnosis of severe ischemic colitis can be secure in the patient in whom ischemic colitis is the only problem, but can become very insecure in a patient who has recently had a major interabdominal operation. Thus some still suggest early resection when ischemic colitis occurs after inferior mesenteric artery ligation.[33,46]

For spontaneously occurring ischemic colitis, the literature[10,13,21,22,24,27,42] contains 12 patients with an angiogram in which occlusive phenomena was present and 15 others with a non-occlusive pattern. We have done angiograms in 19 of our patients. We attempted to categorize the clinical situation of these 46 patients to determine whether or not the presence of an occlusion significantly influenced the clinical features. The truly fulminant cases in which angiography is available show non-occlusion in all 4 circumstances. Of the 6 patients with angiography who had severe disease with stricture and obstruction 4 were non-occlusive and two were occlusive. Clearly transient disease was present in 5 patients with occlusion and in 22 with non-occlusion. Mild stricture was present in 3 with occlusion and in 3 with non-occlusion. There were 3 patients with angiogram, 2 occlusive, one non-occlusive in whom the clinical course is unknown. Thus 69% of the occlusive group had mild disease whereas 53% of the non-occlusive patients had mild disease (not statistically significant). Survival occurred in 65% of those with occlusive and in 66% of those with non-occlusive disease. We interpret this to mean that when the patients are divided according to the presence or absence of arterial occlusion on the basis of angiograms, the clinical reflection of the ischemic colitis process does not differ. Therefore occlusion or non-occlusion is not the basis upon which one can establish either severity or therapy. It must be acknowledged that the possibility that angiography is being done late, and therefore is being done in selective circumstances exists. In our own series the average time for the angiogram was 6 days into the illness. However in 9 patients it was done less than 24 hours into the illness. The groups do not differ one from the other.

Pathogenesis

In their original article, Boley et al.[4] presented experimental evidence to show that a lesion similar to the one seen in their 5 patients could be produced by techniques that interfered with colonic blood supply. Since that time other experimental reports contain confirmatory observations.[5,25,28,30,34] Although there may be minor histologic differences and variations in the rate of progress of the lesion, the end result is the same whether one uses arterial ligation, venous ligation, microsphere injection or partial occlusion complicated by hypotension. Thus it is clear that mechanical interference with colonic blood supply can reproduce the entire spectrum of ischemic colitis. In addition changes in the luminal pressure within the colon can influence colonic blood flow[6,37] in terms of volume flow to the colon, of distributional flow within the colon wall or of nutritional flow to the colon. Finally repeated increases in colonic pressure can induce prolonged decreases in flow with the flow decreases persisting after the luminal pressure increases are removed. By implication the continued presence of such abnormalities of flow might reasonably be expected to produce the same pathologic process as is demonstrated when one interferes with the blood supply by mechanical means. Thus one could speculate that ischemic colitis occurs in patients with some arteriosclerotic change in the colonic vessels plus some process that increases colonic pressure. Perhaps unusual change in colonic pressure is the precipitating event. Such events might explain the ischemic colitis seen with colonic carcinoma.[8,36,37] Some have suggested that ischemia in obstructed colons is much more common than generally agreed[36] and others have been concerned about ischemic perforations of the colon even in the absence of mechanical obstruction.[1,44] Unfortunately the pressures used in the experimental studies are higher than those seen clinically, the presence of a definite process associated with increased colonic pressure is lacking in the vast majority of patients with ischemic colitis, and evidence for advanced arteriosclerosis is not available.[42]

As noted earlier we have been unable to correlate the status of the major arteries with the severity of the ischemic colitis. Thus we are forced to consider factors related to blood flow in the smaller vessels and in the colon wall. The higher incidence of ischemic colitis in the splenic flexure area[26,38] has been presumed to be due to such a distal vessel phenomena with "poorer" blood supply in this watershed area between the superior and inferior mesenteric artery systems. Yet in only two of our 19 cases in which we had both angiographic and barium data was the ischemic process in the watershed between the two arterial systems.[42] Selective arteriography with good visualization of the distal vessels is available in 8 of our own patients and 3 more from the literature, all of whom have non-occlusive disease. None have evidence of smaller arterial occlusions or of venous occlusions.[34] In 4 of the 11 an increased vascularity is documented and in 4 of the 8 where it is commented upon there is decrease in transient time. Expressed differently, 5 patients of the 11 with detailed analysis of the distal circulation have evidence to suggest hyperemia. In none is there any evidence to suggest spasm. Certainly such angiographic observations are not consistent with ischemia. However, ischemia cannot be excluded on this basis for several reasons. First, it is well known that angiographic studies are more representative of the volume present in a vascular bed than of the flow to the organ. Indeed one could speculate that the "increased vascularity" is just a reflection of increased volume due to venous occlusion. However none of the well established angiographic criteria for venous occlusion[34] were found in these patients and further a decreased transient time is inconsistent with venous occlusion. Secondly since we were able to show spasm in the major vessels of our patients with the more extensive disease,[41] we conclude that spasm is not present in our patients with ischemic colitis. In 4 of our 8 patients with distal visualization, the study was within the first 24 hours and since these did not differ from those studied later the time of the study does not seem to be important and probably does not account for the lack of spasm.

The process observed angiographically in the colonic wall is very similar to the hyperemia observed by Boijsen and Reuter[3] in many inflammatory and neoplastic conditions. That it is seen both early and late in the course of the disease is not surprising since reactive hyperemia measured by radioactive microspheres after ligation of bowel vessels was observed both early and late.[47] As we suggested before[42] two of our patients have changes in the location of dye within the wall which could be a reflection of distributional shifts. More observations are necessary before we can even speculate about this possibility. We are forced to conclude on the basis of this review that an ischemic process as the basis for ischemic colitis seen in most patients is not yet established since a detailed evaluation of the blood supply to the involved colon is not consistent with spasm or occlusion. Indeed to date it has only shown evidence consistent with hyperemia. By the same token it must be stressed that these data do not exclude ischemia as the pathologic basis of this process. No better etiology has yet been provided.

Conclusions

Based upon our experience with 55 cases of ischemic colitis and a review of the literature we have concluded that the designation is a useful clinical description which permits the patients' problem to be differentiated from the other known colonic problems. This separation provides a basis for rational therapy which entails observation in the majority of patients, those with mild disease, and resection for those patients who can be shown to have severe disease. A fair prognosis exists for those patients with severe disease and an excellent prognosis for those patients with mild disease. Thus the excellent prognosis is significantly different from diseases such as ulcerative colitis or granulomatous colitis. While the colon lesion can be produced experimentally by a number of manipulations to the blood supply of the colon, available angiographic data do not establish a different clinical course for patients who have occlusion to a major artery as opposed to those with no occlusion. Said differently occlusive phenomena in the major arteries or veins is not an essential feature of ischemic colitis. Angiographic data on the distal vessels often shows only reactive hyperemia. To date no one has established the presence of poor blood flow to the involved colonic wall in a human patient with ischemic colitis. Thus one must question whether or not the pathogenesis of the clinically useful designation, ischemic colitis, includes ischemia.

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DISCUSSION

DR. DAVID B. SKINNER (Chicago): Dr. Williams' extensive experience illustrates the broad clinical spectrum of the disease and, I believe, the advice he has given us about clinical management is sound.

I would like to make a few comments about the etiology. Stimulated by similar patients having various manifestations of ischemic colitis and also by Marsten's report cataloguing these lesions, my colleagues, Dr. Zarins, Dr. Moossa and I have carried out and reported experiments in dogs, and more recently in monkeys, which have some bearing on this question of ischemic etiology.

The full range of lesions which Dr. Williams has described, including ulceration, edema, stricture, fistula, bleeding, perforation and even gangrene, can be reproduced by a temporary occlusion of the vascular pedicle to a loop of bowel.

(Slide) If one isolates a bowel loop at the splenic flexure and places an occlusive clamp temporarily across the base of the pedicle for 6–10 hours, depending on the duration of the occlusion, the full range of different lesions can be seen.

When the clamp is released, arterial pulsation is restored. An arteriogram shows patent vessels. Some of these bowel loops go on to gangrene and necrosis, some enter an intermediate stage with stricture or bleeding, and some make a complete recovery with persistent hyperemia in the bowel wall for several days.

(Slide) We've studied these animals at intervals over a month to six weeks with radioactive microsphere scans, comparing the injured area to adjacent bowel. This is a monkey colon segment that is one month after an eight-hour temporary occlusion.

(Slide) After injection of microspheres and resection of the bowel, a tight stricture can be seen in the ischemic area on this radiograph.

(Slide) The microsphere scan shows that this is a hyperemic lesion at this time, with persistence of the microsphere accumulation in the area at the tight stricture.

Temporary hypoperfusion of bowel can result not only from vascular occlusion but also from low cardiac output and blood pressure or from increased peripheral resistance in the bowel wall. We would like to suggest that the so-called picture of ischemic colitis can be caused by any of these factors but perhaps most likely by a decrease in cardiac output.

After recovery from a transient ischemic episode, the bowel having the greatest vascular resistance may then go on and become permanently damaged, but the healing process itself is a hyperemic as opposed to an ischemic process. This can manifest itself by bleeding and stricture formation or the less severe forms that Dr. Williams has categorized.

The arteriograms in our clinical cases, as well as Dr. Williams and others, have frequently not shown a vascular occlusion.

We have noted, however, that our patients frequently have had severe cardiac disease with a previous myocardial infarction or other reason for a low cardiac output or hypotension sometime in the past. Has Dr. Williams gone into the past history of his cases to check for possible bouts of hypotension preceding the onset of the illness?

We propose that this condition is aptly named. We can demonstrate all these lesions in animal studies by a temporary episode of ischemia which is followed by a reparative process which becomes hyperemic.

Since the etiology in this model is ischemia, until we find some other cause I believe the title of ischemic colitis is correct and can be supported by experimental data.

Dr. James D. Hardy (Jackson, Mississippi): I think that ischemia has a great deal to do with "ischemic colitis" and I align myself with Dr. Skinner and his remarks.

(Slide) This patient was a sheriff in a town about 50 miles away who while on duty suddenly complained of severe abdominal pain. The family physician examined him, felt a small aneurysm, rushed him up to the University Hospital with the provisional diagnosis of ruptured aneurysm. At immediate operation he proved to have fresh clot in his inferior mesentery artery, and I submit that in the future many episodes of abdominal pain will be demonstrated to be due to abrupt occlusion of mesenteric arteries but without intestinal necrosis.

(Slide) If in the course of aneurysm resection one encounters an inferior mesentery artery that seems unduly large, he ought to suspect the possibility that the superior mesenteric and the celiac arteries may be partially occluded and that ligation of the inferior mesenteric artery may produce gut gangrene, especially involving the sigmoid colon. This can be avoided by plugging the inferior mesenteric artery into the fabric graft with which the aneurysm is replaced.

(Slide) This is a man who underwent laparotomy by one of our former residents about a hundred miles away one night. He found a large ruptured aneurysm, closed the abdomen, and sent him to the University Hospital. We reoperated upon him that same night, but we didn't make any special note of the inferior mesentery artery at that time.

(Slide) He came back about a year later with what we at first thought might be a carcinoma of the sigmoid colon producing high-grade incomplete obstruction. We were a little dismayed that we might have missed this lesion at the time of the aneurysm resection, though with all the retroperitoneal hematoma it could easily have been missed at that time.

In any case, this man was obstructed and our radiologist, Dr. Robert D. Sloan, did not believe that the constricting lesion represented carcinoma but that it might represent ischemic change. At uneventful resection it proved to be a benign cicatrizing inflammatory lesion which the pathologists believed compatible with the diagnosis of ischemic colitis.

Subsequent aortography, for hip and thigh claudication, showed that both the hypogastric arteries were severely stenosed. The inferior mesenteric artery was of course already occluded.

(Slide) This is a man we operated upon on Monday of this week for resection of this bleeding constricting lesion of the ascending colon. He has polyarteritis nodosa, and previously had been operated upon for carotid artery occlusive disease producing cerebral ischemia, and for leg ischemia.

He had come in this time with acute abdominal pain. He had gradually improved, passed gross blood, and barium enema had revealed this probable carcinoma. At operation he was found to have several areas of patchy gangrene of a segment of small bowel, plus the right colon lesion, both of which were resected uneventfully.

So, in conclusion, I would say that in our hospital we believe that ischemic colitis is ischemic.

Dr. Paul H. Jordan, Jr. (Houston): We recently had a patient who was in chronic heart failure. He was started on digitalis and, shortly after, he had signs and symptoms of acute abdomen.

(Slide) His splenic flexure was resected for this localized area of infarction which on microscopic section showed viable bowel adjacent to ischemic bowel. The extent of the necrosis was transmural.

(Slide) This shows that the mucosal villi are mere skeletons of the villi of viable bowel and, I think, indicates the early stage of necrosis that existed at the time of operation. We think that the necrosis that occurred in this patient was due to the combination of mesenteric vascular disease, the low flow state occurring in chronic heart failure, and the reduction of mesenteric blood flow due to the vasoconstrictive effect of digitalis.

We are impressed by the experimental work of Dr. Eugene Jacobson who has demonstrated so well the decrease in blood flow to the bowel as a consequence of vasoconstrictive effect of digitalis. One of the previous discussants mentioned the desirability of using a vasodilator drug such as papanarin in patients with suspected ischemic colitis. Other drugs currently on the scene which may prove valuable in preventing mesenteric vascular constriction are prostoglandius and glucagon.

Dr. Edward E. Mason (Iowa City, Iowa): Dr. Williams, we have seen a couple of instances recently of a very severe chemical colitis which has been reported in the literature, which I think might be confused with this picture. You see the thumb-printing and it may be necessary to resect the bowel to save the patient's life.

Did any of these patients have clindomycin?

Dr. Thomas V. Santulli (New York, New York): Although I don't have any data on this entity in the age group presented, Dr. Williams, the pathology of neonatal acute necrotizing enterocolitis in which the hallmark is coagulation necrosis on the basis of selective mesenteric ischemia because of some episode of hypoxia or other stress is identical to the lesion you have described.

In addition, the stricture that you see in these ischemic colitis patients also occurs in acute necrotizing enterocolitis, 5-7 weeks after the acute episode.

We've had three instances in 69 patients in the very young age group. I don't think it's necessary to show evidence of vascular occlusion at the time that the final lesion is seen. We have explained it on the basis of cicatricial healing following the pathologic events initiated by the selective mesenteric ischemia.

Dr. William W. Krippaehne (Portland, Oregon): I rise to ask a question of Dr. Williams because of some studies we have done at our institution; Dr. Jack Campbell, Professor of Pediatric Surgery, encountering ischemic colitis in the newborn has studied ischemia produced primarily by hypoxia, but by hypovolemia as well, in the small labrador puppy to identify the early changes that occur.

In this group of labrador dogs on 7% oxygen with a Po_2 level of 20 at two hours, the lesions they demonstrated were those of fibrin platelet aggregation, leukocyte entrapment in capillaries and small venules. They demonstrated early endothelial blistering, loss of tight junctions with ultimately destruction of endothelium of this microvasculature. These changes were in the same distribution as one sees in ischemic colitis, or necrotizing colitis of the newborn. The changes that showed up early were ultrastructural and they look similar to the microvascular changes of shock lung.

I wonder if Dr. Williams had done any early ultrastructural studies in any of his cases.

Dr. Kenneth G. Swan (Newark, New Jersey): I think one of the problems that has led to the conflict of whether or not this lesion is an ischemic one as Dr. Williams now suggests, is the interpretation of our only available technique for measuring flow to this organ during the disease process and that is angiography. Clearly it is a poor tool at best.

For example, if resistance across the mesenteric vascular bed falls and arterial pressure remains constant, we would expect to find a decrease in the calibre of the blood vessels supplying the gut.

Conversely, if there was a vasoconstrictor response at the microcirculatory level, we would see an increase in the calibre of the arteries supplying the intestine, even though there might be little or no flow through the gut.

I think Dr. Williams has observed a possible etiologic mechanism in histologically describing what he calls "stasis of the vasculature" of the gut. Assuming this is arterial dilation, then maybe there is a decrease in flow or obstruction to flow at the venous side of the mesenteric circulation. ischemia and vasodilation can exist concurrently.

Since most of these lesions are on the left side of the colon, I would like to ask Dr. Williams if it is not possible to biopsy the mucosa and perhaps get more insight into microcirculatory events during the disease process.

DR. LESTER F. WILLIAMS, JR. (Closing discussion): On an emotional basis I agree with the discussants that this must be ischemia. However, I must stress that to date this ischemia has not yet been documented in patients.

As Dr. Skinner knows, part of the reason this lesion is called ischemic is that one can produce this in dogs, monkeys and rabbits by interfering with an artery, the veins, the microcirculation, or by partial occlusion of vessels hypotension. There's no question whatsoever that this is true.

With respect to his question about hyperemia and healing; we were concerned that hyperemia was the basis for the vascularization that we found. Our average time for our angiograms was six days, but we had nine patients in whom we did angiography within 24 hours of the onset of the disease. Since we have had 27 in whom we have done angiograms for extensive bowel ischemia and have often shown evidence of spasm, we concluded that by not showing spasm in any of these patients, spasm was not present, at least using the angiographic method.

In most of our 70 cases of extensive disease, we have been able to show precipitating illness, chronic congestive heart failure, digitalis toxicity, etc. These are not prominent features of these patients with ischemic colitis, although there is an occasional patient, as I mentioned, in whom ischemic colitis is incidental to other severe disease.

Dr. Hardy, with respect to the cases of stenosis of the colon due to ischemia, I'm sure that it occurs. The issue is, however, how commonly does it occur and how commonly does it process. After all, this progression is the basis for the suggestion in the literature that they should all be resected as soon as the stenosis is seen.

I've suggested that there are seven reports in the literature where the process goes on to severe stenosis. There are an equal seven where the patients "cure" themselves. As nearly as I can tell from what's available in the literature, these patients are not different one from the other at the time of their initial stricture. That's my concern.

I believe it is now adequately shown that carcinoma can be excluded by endoscopy.

With respect to Dr. Jordan's question, we have seen a patient who has extensive bowel disease after digitalis but we have not found digitalis to be an important factor in these patients. Clearly the experimental evidence in dogs and monkeys as well as some data in people shows that digitalis can induce changes in the splanchnic circulation.

I'm not clear in my own mind on the place of vasodilatation in ischemic colitis. We do use it as have many others for extensive bowel ischemia. You may recall from that complicated slide that I used in discussing John Bergan's paper that we use vasodilators in all kinds of situations with extensive ischemia, but not yet in this lesion.

Dr. Mason, with respect to the clindomycin problem, we have seen two cases of colitis secondary to this drug. We've not studied them the same way we did this group. They didn't happen to have thumb-printing and so on, so I did not include them in this group. Perhaps the two are related one to the other.

Dr. Santulli, acute necrotizing enterocolitis is very similar to what we call extensive acute ischemic bowel disease. We make a rather specific separation between these two as they are clinically separate lesions. There's no question that both lesions can go on to stricture in a few patients.

It's also quite clear, as you suggested, that the pathology of the involved bowel is identical. No matter how you get there, whether you interfere with arteries, veins or both, or do it with hypoperfusion, the histology cannot separate any of these lesions one from another. That's part of our difficulty.

I agree completely with Dr. Swan's suggestion that angiography is not a secure way to show flow and, in fact, I agree that we are probably showing a redistribution of flow which may make this lesion legitimately ischemic. As he knows, auto-regulation and auto-regulatory escape which is the phenomenon he was alluding to, with respect to the small intestine, do occur in the colon. We have data to suggest that in the presence of severe changes in flow, severe changes in pressure, both auto-regulation and auto-regulatory escape continue to be present. We cannot, however, evaluate the effects of such changes in flow patterns because we haven't been able to experimentally document varying degrees of ischemia to bowel. In addition, we do not know whether bowel which has been damaged does or does not continue to exhibit these phenomena. We haven't been able to make a preparation which lets us evaluate this yet.

And, then, lastly, the issue of the newborn or the puppy who has small vessel involvement: we have looked at this experimentally ourselves and at least down to the 50μ level can show no abnormalities with respect to flow.

We have not looked at ultrastructure. We've looked at biopsies with respect to tetrazolium studies, at histologic studies; with respect at pH of the serosa and mucosa, and also at electromyography. Let me summarize by saying that when we pull all these together experimentally we're unable to equate any of them with either the degree of ischemia or with the distribution of flow. Thus I remain unable to separate all these lesions one from another.

Comparison of Long-term Results of 364 Femoropopliteal or Femorotibial Bypasses for Revascularization of Severely Ischemic Lower Extremities

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Successful revascularization of the severely ischemic lower extremity can be achieved by femorotibial as well as femoropopliteal bypass. The incidence of delayed graft occlusion after salvage of the severely ischemic lower extremity is low in patients with femorotibial or femoropopliteal bypass. Femorotibial bypass was performed in over one-third of patients undergoing bypass. Tibial bypasses resulted in effective prolonged revascularization of the severely ischemic lower extremity. An aggressive diagnostic and therapeutic approach to revascularization of the severely ischemic lower extremity can result in prolonged limb salvage by tibial or popliteal bypasses in lieu of primary amputation.

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THE FEASIBILITY of limb salvage by distal bypasses to the popliteal or tibial artery has been demonstrated. Although considerably less experience has accumulated with bypasses to the tibial or peroneal arteries than with bypasses to the popliteal artery, successful revascularization in a limited number of bypasses has been reported.[1,2,7,9,11,12,14,18,19] Long-term followup has recently become available in which prolonged bypass function and delayed graft closure following bypasses to the popliteal or tibial arteries was studied and compared to an intra-institutional experience with standard femoropopliteal bypasses.[15] Although a lower incidence of initial graft function and a lower incidence of initial limb salvage occurred in patients requiring distal small vessel bypass as compared to results of femoropopliteal bypass, the rate of delayed graft occlusion after distal bypass was found to be low and prolonged limb salvage was demonstrated. In this study, experience with long-term graft function and limb salvage in 364 patients with severe ischemia of the lower extremity is presented. In most patients, revascularization was performed in lieu of primary amputation in extremities afflicted with gangrene, ischemic ulceration, or rest pain. In some patients, limiting claudication was considered an indication for operation. The followup is extended to 11 years to determine the duration of limb salvage and the early and delayed mortality in patients with arterial insufficiency undergoing bypass in lieu of primary amputation.

Methods

Evaluation of Arterial Insufficiency

Standard clinical tests were the basis of diagnosis in patients with arterial occlusion and probable associated arterial insufficiency of the lower extremity. Diagnosis of peripheral ischemia was suspected in most patients by the characteristic history of claudication or rest pain, or by presentation with varying degrees of tissue loss (ischemic ulceration, gangrene). Trophic changes, and diminished or absent distal pulses further substantiated the suspicion of peripheral arterial insufficiency. In patients

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This work was done in part during the tenure of an Established Investigatorship of the American Heart Association (Dr. Reichle).

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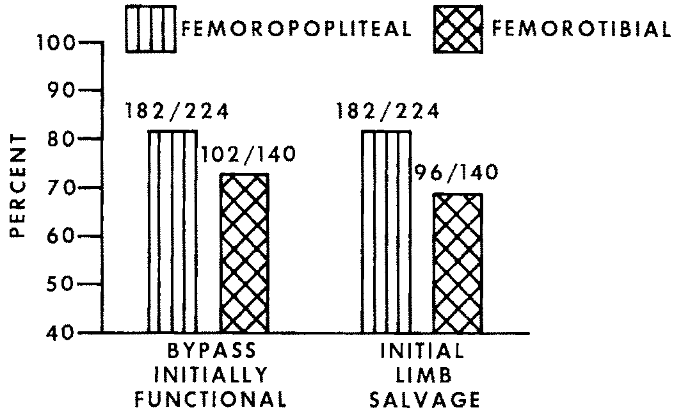

FIG. 1. Incidence of bypass function and limb salvage.

manifesting these signs or symptoms, the best tests to confirm the presence of arterial insufficiency are demonstration of pallor on elevation, rubror of dependency and prolongation of the venous filling time. Arteriograms did not serve to substantiate the clinical diagnosis but were performed in order to precisely delineate the anatomy of the known arterial occlusion. Particularly in diabetic patients, the differential diagnosis of extremity pain includes neuropathy; nevertheless, in this relatively common situation the aforementioned clinical findings were most consistent and allowed definitive demonstration of concomitant arterial insufficiency.

Technic of Femoropopliteal Bypass

Reversed autogenous saphenous vein was used for femoropopliteal bypass whenever adequate vein was available. If saphenous vein was not available or if the ipsilateral and contralateral veins were insufficient, woven Dacron, 8 mm, was used for bypass. Anastomosis was performed either proximal or distal to the knee joint on the basis of the preoperative arteriogram. Both Dacron as well as autogenous saphenous vein bypasses were carried to the distal popliteal artery if the proximal artery was absent or diseased on preoperative arteriogram and/or on operative inspection. When feasible, proximal popliteal bypass was preferred to distal popliteal bypass. Similarly, whenever possible, bypass to the proximal or distal popliteal artery was preferred over distal bypasses to tibial or peroneal arteries. All anastomoses were end-to-side, both proximally and distally. When saphenous vein was available, the vein was distended by manual saline injection.

Technic of Femorotibial Bypass

Selection of site of distal anastomosis was predicated primarily by preoperative arteriographic appearance of the available run-off. Femorotibial bypass was performed when popliteal artery was not patent. In a few patients, bypass was electively carried to the tibial artery when preoperative arteriogram showed popliteal artery patency but associated severe disease which was extensive and obvious on arteriogram. Reversed autogenous saphenous vein was used in all except four bypasses in which 8 mm Dacron tubing was employed. Bypasses were end-to-side from common femoral or superficial femoral artery proximally to anterior tibial, posterior tibial or peroneal arteries distally.

Determination of Graft Function

Graft function was assessed in most cases by palpation of distal pulses. If patients were geographically unavailable, followup was achieved by telephone conversation with the referring physician.

Selection of Patients for Review

Review of bypasses was performed in 364 consecutive femoropopliteal or femorotibial (or peroneal) bypasses done as a single procedure. When bypasses were performed in conjunction with proximal arterial reconstruction (e.g. aorto-iliac, aorto-femoral bypass) femoropopliteal or femorotibial bypasses were not included in this review. All patients operated for signs and symptoms of severe ischemia by femoropopliteal or femorotibial bypass between 1963 and 1974 inclusive were included in this review.

Results

Initial Graft Function and Initial Limb Salvage

Bypasses were considered initially functional if definite clinical evidence of graft function persisted at least 8 weeks postoperatively. Usually this included palpable distal pulses, but definite evidence of improved arterial tissue perfusion (e.g. symptoms, temperature, loss of pallor of elevation, loss of dependent rubror) was considered a prerequisite of bypass patency. An extremity was considered initially salvaged if it had been rendered functional by a bypass for over 8 weeks. The initial results with femoropopliteal bypass were: functional bypass and limb salvage, 182 of 224 (81.2%). The corresponding initial results of femorotibial bypass were: functional bypass, 102 of 140 (72.8%); limb salvage, 96 of 140 (68.6%) (Fig. 1).

Mortality

The mortality rate as listed relates to patients dying within the first 6 weeks after operation. It pertains to any patient in whom the initial operation was bypass to popliteal, tibial or peroneal arteries and includes those patients in whom subsequent extremity amputation was performed. Mortality occurred in 7 of 224 (3.1%) patients after femoropopliteal bypass and in 4 of 140 (2.9%) patients undergoing femorotibial bypass. Mortality in these 11 patients was primarily related to cardiac disease and as expected was similar in both groups. Delayed deaths are reviewed above in discussion of long-term results.

TABLE 1. *Long-term Results in Patients in Whom Initial Limb Salvage Was Achieved and in Whom Followup is Available.*

	One to 11 Years Followup (1963-1974)		Four to 8 Years Followup (1967-1971)		Eight to 11 Years Followup (1963-1966)	
	Femoropopliteal	Femorotibial	Femoropopliteal	Femorotibial	Femoropopliteal	Femcrotibial
Living, Limb Salvage	76/167 (45.4%)	45/86 (52.3%)	25/58 (43.1%)	15/40 (37.5%)	9/59 (15.3%)	4/16 (25.0%)
Died, Limb Salvage	50/167 (29.9%)	26/86 (30.2%)	14/58 (24.1%)	15/40 (37.5%)	31/59 (52.5%)	8/16 (50.0%)
Late Graft Occlusion	41/167 (24.6%)	15/86 (17.4%)	19/58 (32.8%)	10/40 (25.0%)	19/59 (32.2%)	4/16 (25.0%)

Incidence of Diabetes Mellitus

Somewhat less than one-half (168 of 364, 46.2%) of patients operated were diabetic. Seventy-six of 140 (54.3%) of patients requiring femorotibial bypasses were diabetic; 92 of 224 (41.1%) were diabetic. In patients requiring femoropopliteal bypass, the incidence of initial graft function was similar in diabetic patients (74 of 92 or 80.4%) as compared to non-diabetic patients (108 of 132 or 81.8%). In patients requiring femorotibial bypass, initial graft function averaged somewhat lower in diabetic patients (51 of 76 or 67.1%) as compared to non-diabetic patients (51 of 64 or 79.6%).

Indications for limb revascularization. Rest pain, gangrene or ischemic ulceration was the indication for operation in most patients. In some patients limiting claudication, usually occupational, was considered indication for bypass to either popliteal or tibial artery. In 224 patients undergoing femoropopliteal bypass, the indications were: gangrene, 65; ischemic ulceration, 38; rest pain, 77; claudication, 44. In 140 patients undergoing femorotibial bypasses, the indications were: gangrene, 54; ischemic ulceration, 28; rest pain, 47; claudication, 11. Thus, 310 of 364 (85.1%) bypasses were performed in the presence of severe ischemia (gangrene, ischemic ulceration, or rest pain).

Patient Followup

Followup was complete except for 25 of 364 (6.9%) of total patients, and 15 of 224 (6.7%) of femoropopliteal bypasses and 10 of 140 (7.1%) of femorotibial bypasses. The current status of patients in whom initial limb salvage was achieved is shown in Table 1.

Patients with initially functioning bypasses and in whom limb salvage was achieved were studied in relationship to three groups: 1) patients who are presently alive with functional bypasses and limb salvage; 2) patients who have died with functional bypasses and limb salvage at the time of death; 3) patients in whom bypass had undergone delayed occlusion. Operations in this review were operated from 1963 and 1974 inclusive, and thus followup extends up to 11 years. To study interval prolonged followup, the patients were divided into subgroups according to the year of operation. In addition results of femoropopliteal and femorotibial bypasses were compared by the life-table technique (Tables 2 and 3).[20]

Current Incidence of Limb Survival and Graft Patency in Surviving Patients

The incidence of graft patency and patient survival is shown in Fig. 2. Graft patency associated with patient survival is comparable in patients after femoropopliteal and femorotibial bypass. The incidence of bypass patency and associated patient survival after 8 to 11 year followup is 15.3% (9 of 59) after femoropopliteal bypass and 25% (4 of 16) after femorotibial bypass. These figures include only patients in whom continued graft function and limb survival with patient survival was achieved. This does not include patients in whom limb salvage was

TABLE 2. *Long-term Patency of Femoropopliteal Bypasses to Severely Ischemic Lower Extremities**

Interval (mon)	No. Bypassed Extremities at Risk	No. Bypasses Failing	No. Bypasses Not Observed Throughout Interval Due to:		Failure Rate In Interval (%)	Patency Rate In Interval (%)	Accumulated Patency Rate (%)
			Death	Duration of Followup			
0-12	224	58	16	25	28.5	71.5	71.5
13-24	125	6	16	14	5.5	94.5	67.6
25-36	89	2	7	3	2.4	97.6	65.9
37-48	67	6	2	7	9.6	90.4	59.6
49-60	52	1	4	7	2.2	97.8	58.3
61-72	40	2	5	7	5.9	94.1	54.9
73-84	26	1	3	3	4.3	95.7	52.5
85-96	19	0	1	9	0	100	52.5
97-108	9	0	2	3	0	100	52.5
109-120	4	0	0	1	0	100	52.5
121-132	3	0	0	0	0	100	52.5

*Modified From Wheelock and Filtzer.[20]

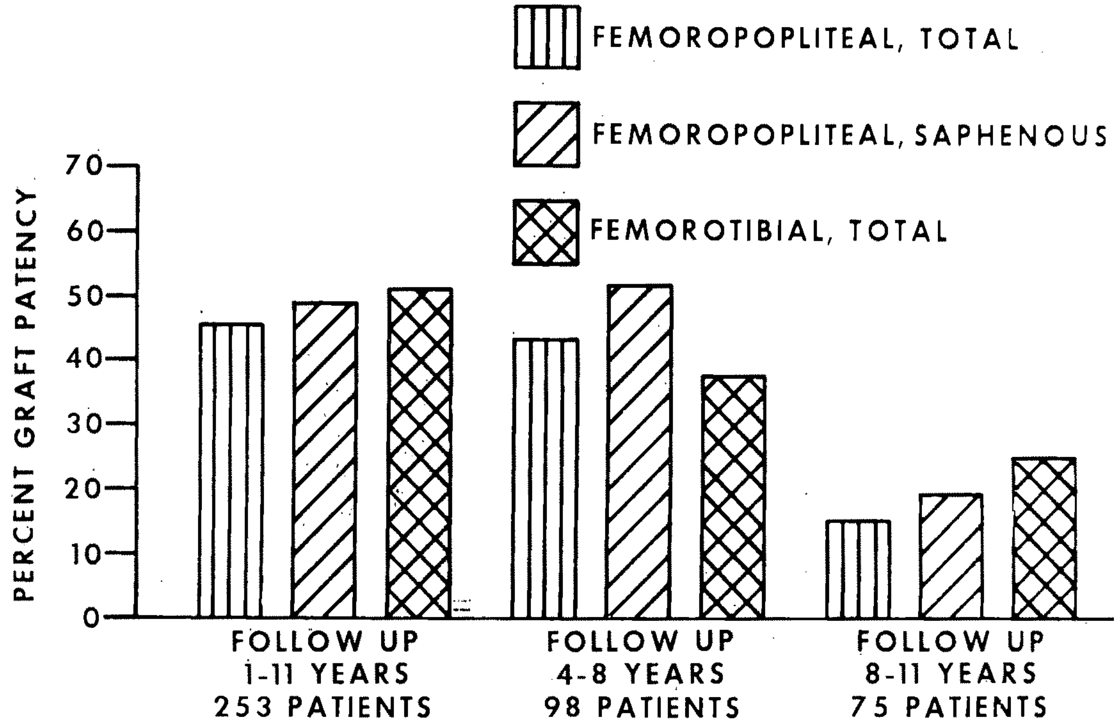

FIG. 2. Current incidence of patient survival, graft patency and limb salvage (per cent of surgically treated patients in whom followup is available and who are presently alive with limb salvage and graft function).

maintained until the time of the patient's death from other reasons (Fig. 5). Long-term patency of femoropopliteal bypasses are divided into prosthetic grafts and autogenous vein grafts for comparison, inasmuch as femorotibial bypasses were performed almost exclusively with autogenous saphenous vein. Although femorotibial bypasses had a lower rate of initial bypass patency the long-term patency rate of femorotibial and femoropopliteal bypasses is comparable.

Delayed Graft Occlusion.

Late graft occlusion in patients in whom initial limb salvage was achieved was relatively low (Fig. 3). In the total followup experience, delayed graft occlusion occurred in 24.6% (41 of 167) patients after femoropopliteal bypass and in 17.4% (15 of 86) of patients undergoing femorotibial bypass (Fig. 3 and Table 1). Average incidence of delayed bypass occlusion up to 11 year followup is comparable to those in patients followed up to 8 years reported in our earlier review.[15]

Bypass Function, Delayed Mortality and Delayed Graft Occlusion in Total Series

Approximately one-half of all operated patients are currently alive with functional bypass (Fig. 4). After femoropopliteal bypasses, 45.5% (76 of 167) patients are alive and have functional bypasses; of patients in whom saphenous vein graft was performed to the popliteal artery, 57 of 118 (48.3%) are presently alive with patent bypass. Similarly, patients who have undergone femoro-

TABLE 3. *Long-term Patency of Femorotibial Bypasses to Severely Ischemic Lower Extremities**

Interval (mon)	No. Bypassed Extremities at Risk	No. Bypasses Failing	No. Bypasses Not Observed Throughout Interval Due to: Death	Duration of Followup	Failure Rate In Interval (%)	Patency Rate In Interval (%)	Accumulated Patency Rate (%)
0-12	140	44	13	23	36.1	63.9	63.9
13-24	60	0	6	8	0	100	63.9
25-36	46	3	4	9	7.6	92.4	59.1
37-48	30	2	2	11	8.5	91.5	54.1
49-60	15	0	3	2	0	100	54.1
61-72	10	0	0	1	0	100	54.1
73-84	9	2	0	2	25.0%	75	40.5
85-96	5	0	0	1	0	100	40.5
97-108	4	0	1	1	0	100	40.5
109-120	2	0	0	1	0	100	40.5
121-132	1	0	0	0	0	100	40.5

*Modified From Wheelock and Filtzer.[20]

tibial bypasses currently are alive with functional bypass in 52.3% (45 of 86) of cases.

Incidence of Patients in Whom Bypasses Are Currently Patent and Patients Who Have Died with Patent Bypasses

After femoropopliteal bypass (4 to 8 years followup) 67.2% (39 of 58) are currently alive with patent bypasses or have died with patent bypasses (Fig. 5). In patients with autogenous vein bypass to the popliteal artery, 78.9% (30 of 38) are currently functional or have died with limb salvage. After femorotibial bypass, 30 of 40 (75.0%) of patients are alive with limb salvage or have died with patent bypasses (4 to 8 year followup). After 8 to 11 year followup, the corresponding figures remain quite similar: femoropopliteal, saphenous, 71.4% (30 of 42); femorotibial, 75.0% (12 of 16). These figures indicate that most patients undergoing bypass for limb-threatening ischemia benefit substantially from revascularization to the tibial or popliteal arteries with current limb salvage in living patients or until the time of death in patients dying from other causes.

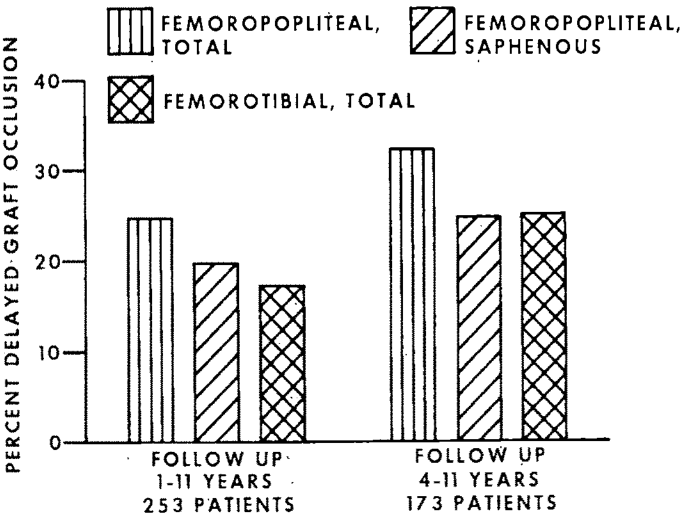

FIG. 3. Current incidence of delayed graft occlusion (per cent of surgically treated patients who achieved initial limb salvage and who are available for followup information).

Discussion

Indications for Bypass to Popliteal, Tibial or Peroneal Arteries

Severe ischemia of the lower extremity, including rest pain, gangrenous ulceration or gangrene was considered an absolute indication for attempts at revascularization, including thorough preoperative arteriograms. These indications were present in the majority of our operated patients (see Results). In some patients claudication is a relative indication for aggressive therapeutic approach; if claudication prohibits occupational performance, there is little question that revascularization should be considered. If claudication does not greatly interfere with a given patient's daily activities, the patient can be observed to determine whether progression of the symptoms eventually will occur. A more conservative approach is generally indicated in patients in whom only distal run-off is present and in whom revascularization requires femorotibial or femoroperoneal bypass. In comparing initial patency rates from different series, the severity of the preoperative indications should be considered in assessing the success of revascularization.

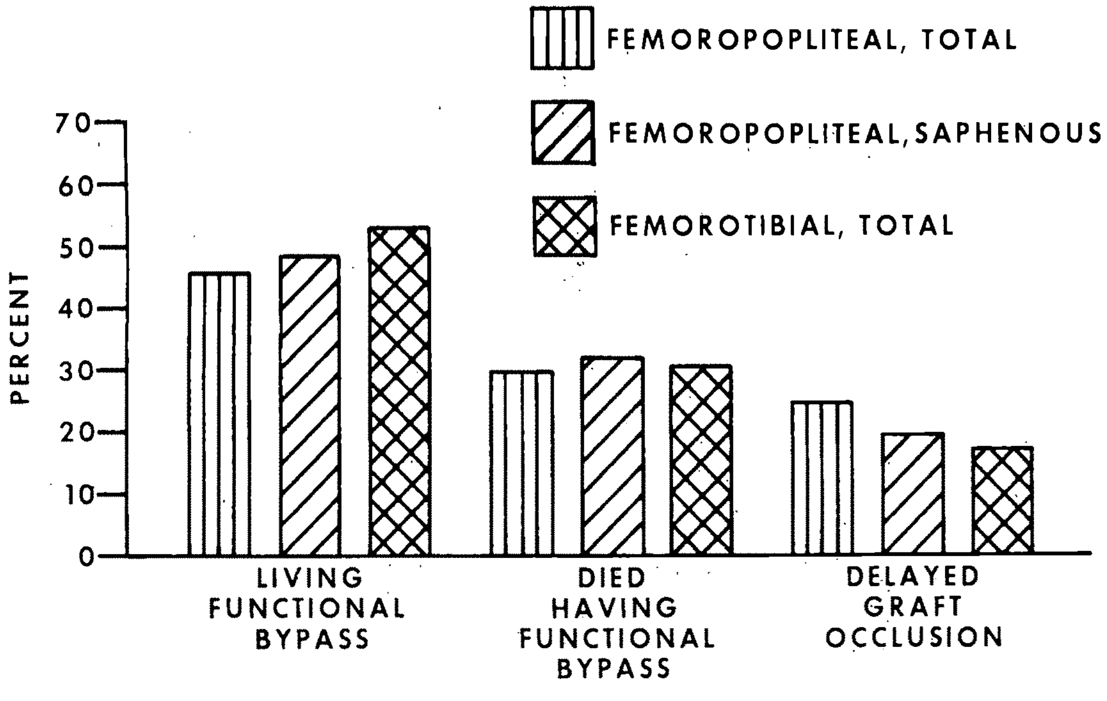

FIG. 4. Incidence of bypass function, delayed mortality, and delayed graft occlusion in total series of patients in whom initial limb salvage was achieved and in whom followup is available.

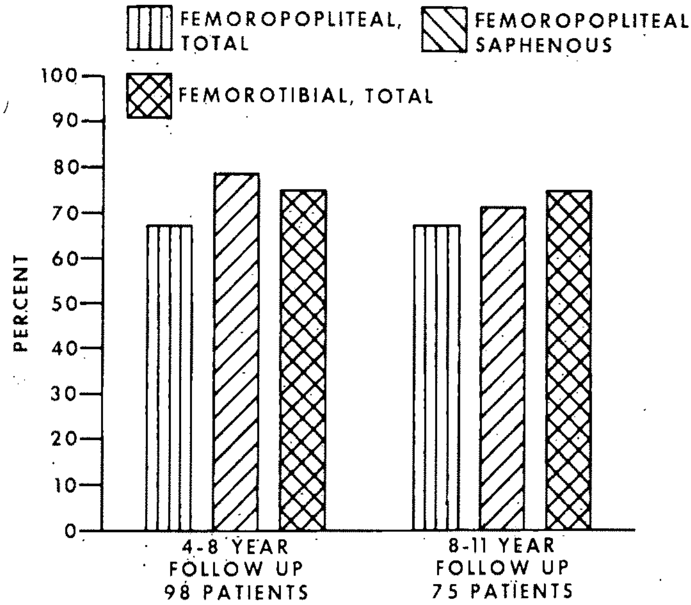

FIG. 5. Long-term followup of patients achieving initial limb salvage after bypass (per cent of surgically treated patients who achieved initial limb salvage and who are presently alive with limb salvage and graft function or who had limb salvage and graft function at the time of death).

Relative Frequency with Which Bypasses to Tibial Arteries or to Popliteal Arteries Are Required

Bypass to tibial or peroneal arteries was found to be necessary in 38.5% of total series (140 of 364), and femoropopliteal bypasses were feasible in 61.5% (224 of 364) of patients. As a more aggressive diagnostic approach to patients with severe extremity ischemia is followed, an increasing number of ischemic limbs will be bypassed to the smaller distal arteries, and fewer primary amputations will be performed. Carefully performed preoperative arteriograms are required to delineate patent distal small arteries to which bypasses can be performed for extremity revascularization. Demonstration of small collateral blood vessels generally suggests an adequate arteriogram has been performed. Because of the variability of the velocity of flow in the ischemic lower extremity, it is frequently necessary to perform more than one injection of contrast and to film distally at varying time intervals to demonstrate distal arterial runoff. Thoroughly performed arteriograms will undoubtedly result in more distal bypasses and fewer primary amputations.

The Problem of Inadequate Autogenous Vein

In the majority of patients an adequate autogenous saphenous vein is available for bypass to the popliteal or tibial arteries. Frequently, the adequacy of a vein for distal bypass cannot be ascertained until the vein has been removed and attempts at dilitation have been made. On the basis of histologic studies and clinical impressions we believe that the trauma of forceful dilatation of the vein to be used for bypass is preferable to a non-dilated vein of smaller diameter, inasmuch as a vessel of smaller diameter will have higher resistance to flow. Cephalic vein is an acceptable alternative to saphenous vein, but may not be of sufficient length to bypass to the distal arterial tree. Despite existing alternatives at obtaining autogenous, viable vein of adequate length and diameter for bypass to distal small arteries, a persistent number of patients will continue to require amputation primarily because of lack of an entirely adequate arterial substitute capable of function under conditions of low blood flow to the distal arterial tree. This problem remains an important area for continued investigation. Possible alternative arterial substitutes now under active investigation include die-grown reinforced arterial grafts (Spark's Mandrils) in which autogenous tissue is grown around a rubberized silicone rod which is surrounded by loose-mesh Dacron lattice for support.[19,20] Pretreated umbilical vein is now being tested for its possible application as a conduit for small vessel bypass,[21] additionally modified bovine heterografts and fresh venous allografts have been used as alternative arterial substitutes.[22–24]

Technical Modifications in Bypasses to the Distal Arterial Tree

The distal arteries can be readily approached through medial (posterior tibial peroneal) or lateral incisions without resection of bone and with minimal muscle separation. Other exposures have been suggested including a lateral approach to the tibial-peroneal arteries.[25] Successful double bypass, employing proximal Dacron and distal saphenous vein has been reported.[26]

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DISCUSSION

DR. JOHN A. MANNICK (Boston): I certainly agree with Dr. Reichle that it is possible to achieve good late results in patients with severe ischemia with femoral tibial bypass vein grafts. I would like, however, to point out one other option sometimes available in these individuals.

Dr. Davis and I recently reviewed our personal experience with a series of patients operated upon for limb salvage who had distal popliteal artery occlusion. The surgeon in some of these individuals has the choice of putting the distal anastomosis of the vein graft either into an isolated popliteal artery segment which is not directly connected with any of the tibial vessels because of popliteal artery occlusion distally, or of placing the distal anastomosis of the vein graft into a tibial vessel, one or more of which may be patent in the calf.

We found that we had operated on 55 patients with distal popliteal artery occlusion and we had done femoro-tibial bypasses in 38 of them and isolated segment popliteal artery bypasses in 17.

Interestingly enough, while the early patency rate of the isolated segment popliteal artery vein grafts was better, the late patency of both kinds of grafts was approximately the same, 60–70%, not very different from what Dr. Reichle has told us this morning.

Both these kinds of patients have somewhat worse late results in our experience than approximately 200 conventional femoro-popliteal bypasses performed in the same period of time by the same surgeons.

We would conclude that, when the surgeon has the choice of doing an isolated segment vein graft, or a femoro-tibial vein graft, in spite of the temptation to get the blood down to an artery that's really connected to the foot, the femoro isolated popliteal segment bypass may be the procedure of choice because of its greater simplicity.

DR. EMERICK SZILAGYI (Detroit): The membership will perhaps be interested in a form of presentation of late results different from that used by Dr. Reichle in his fine essay. The trends in the patency of reconstructive operations may be more readily perceived from graphs constructed with the method of life table analysis.

(Slide) This slide states the composition of the clinical material on which we based our study. The clinical material was closely similar to that presented by the previous essays but two differences must be pointed out. First, in our nomenclature the adjective "femoropopliteal" is applied to those operations in which the distal anastomosis is placed in the popliteal artery below the level of the knee joint. The operations performed on branches of the popliteal artery are designated as infrapopliteal procedures. Secondly, all the grafts that we surveyed were autogenous saphenous vein transplants.

(Slide) The results are expressed as patency rates. In vascular surgery a patent graft is virtually always equivalent to a successful operation. It should be further stressed that the patency in these cases was always checked and verified by angiographic methods.

As regards femoro-popliteal operations, an inspection of the patency curves shows that there is a remarkably steady rate of attrition of patency rates. One might almost call this decay curve a biological constant. The broken line represents those observation periods during which, at the time of the analysis, the number of cases allowed only tentative statistical analysis. Since then, these groups have also been filled out and the trend of the curves has remained approximately unchanged. At four years of observation the patency rate is 76%, at six years it is 58%, and at eight years it is 45%. The deterioration of the results of infrapopliteal operations is at a considerably faster rate.

There is a suggestion that in the later observation periods the good results of the infrapopliteal operations persist with a slightly greater constancy.

These patency rates may appear somewhat disappointing but, compared to those of any other reconstructive method in the femoropopliteal area, they are far superior. Their study does serve, however, to warn against undue optimism regarding late results.

DR. RONALD J. STONEY (San Francisco): We, too, have been concerned about the causes of late graft occlusion. In our experience with femoro-popliteal grafts, most late failures occurred because of progressive obliterative disease of the tibial vessels beyond the graft. I wonder if Dr. Reichle examined the causes of late graft occlusion in his series, and could tell us how many were due to progression of atherosclerosis in the tibial arteries.

DR. FREDERICK A. REICHLE (Closing discussion): Over ten years ago, Dr. Mannick demonstrated significant patency and limb salvage using saphenous vein bypasses into popliteal segments in patients having no direct popliteal artery outflow tract in continuity. This appears a good alternative to tibial bypass, although the lack of direct distal arterial run-off may in the long run prevent prolonged function. We would, in fact, much prefer bypassing to a popliteal segment rather than to a tibial artery if a sufficiently long autogenous vein of adequate diameter as judged clinically is not available. The preoperative arteriogram is important in reaching a decision as to the site of distal bypass in all these patients.

As Dr. Szilagyi has appropriately pointed out, the life table analysis is of importance and it is included in the manuscript. The figures of our five-year cumulative patency rate are 54.9% patency for femoropopliteal bypass after 61–72 months and 54.1% after femorotibial bypass. Subsequently drop-off is low and cumulative patency is 40% even after 120 months.

The causes of late graft occlusion are of great interest and we have the impression, in fact, that it is the progression of atherosclerosis obliterans in the distal run-off that causes eventual occlusion of most bypasses to the popliteal as well as to the distal tibial vessels. However, we have also seen a few patients with femoroperoneal or femorotibial bypasses in whom there was little doubt that primary saphenous vein graft failure occurred. Stenosis of functional vein graft was seen on arteriograms. Histologic sections show a thickened saphenous vein. This is a less common problem compared to failure of distal arterial run-off.

The problem of unavailability of an adequate autogenous saphenous vein is certainly a very important one. We have not found the standard Dacron prostheses used to bypass to the tibial arteries to be successful, and we are interested in such approaches as autogenous tissue tubes grown around Dacron enforced mandrils or previously arterialized cephalic vein as possible alternatives for bypasses to distal arteries.

Ex Vivo Renal Artery Reconstruction

FOLKERT O. BELZER, M.D., OSCAR SALVATIERRA, M.D., ALPHONSE PALUBINSKAS, M.D., RONALD J. STONEY, M.D.

Ex vivo renal artery reconstruction and autotransplantation is a relatively recent addition to the surgical armamentarium for renal vascular hypertension. Ten consecutive patients were considered for this surgical therapy and form the basis of this communication. The patients were treated by a combination of methods including bilateral *ex vivo* reconstruction, unilateral *in situ* and contralateral *ex vivo* reconstruction, and unilateral *ex vivo* reconstruction and contralateral nephrectomy. Replacement of the diseased segment of the renal artery in all *ex vivo* reconstruction consisted of arterial autografts including hypogastric artery, splenic artery, common iliac, and external iliac artery. In the *ex vivo* reconstruction, the ureter was either left intact or was transected and reconstructed by standard ureterovesicle implantation. After surgery all patients became normotensive without antihypertensive medication. Although this is a relatively small series, the uniform good results in these patients with extensive disease suggest that *ex vivo* renal artery reconstruction is a safe and effective method of treatment. Thus, it should be more widely applicable, especially in those patients with renal vascular disease who were previously thought to be inoperable or eligible for nephrectomy only.

FIBROMUSCULAR DYSPLASIA of the renal arteries is usually confined to the main renal artery and is repaired by *in situ* vascular reconstructive techniques. However, when fibromuscular dysplasia extends into the branches of the renal artery, *in situ* reconstruction may be difficult, hazardous, or impossible. In these instances, temporary nephrectomy and *ex vivo* repair with microvascular techniques followed by autotransplantation allows the precise repair of such lesions.[2]

Ten consecutive patients with renovascular branch lesions underwent microvascular arterial reconstruction using *ex vivo* techniques between 1972 and 1975. Indications for surgery were uncontrollable hypertension on a maximal medical regimen in all but one patient who had a symptomatic aneurysm in a solitary kidney. All were evaluated by the vascular service at the University of California, San Francisco. They are summarized in Table 1 and were considered inoperable by *in situ* methods. Five cases are described below in detail to emphasize variations in pathology and surgical approach.

From the Departments of Surgery and Radiology,
University of California, San Francisco
and the Department of Surgery,
University of Wisconsin, Madison, Wisconsin

Case Reports

Case 1. A 42-year-old caucasian woman was first noted to be hypertensive four years prior to admission. In January, 1973, renal arteriography showed severe fibromuscular dysplasia of both renal arteries (Fig. 1). The primary branches of the left kidney showed severe disease with aneurysmal dilatation and *ex vivo* reconstruction of this kidney appeared to be indicated. The stenosis in the right kidney involved a segment of the renal artery distal to the first bifurcation but, as no branch arteries were involved, *in situ* reconstruction appeared feasible. In February, 1973, a left *ex vivo* reconstruction was performed using the hypogastric artery and a right *in situ* repair using an interposition of autologous saphenous vein (Fig. 2). The patient refused a postoperative arteriogram and was normotensive until 9 months after surgery at which time she became hypertensive again. Arteriography showed a normal appearing left renal artery but showed stenosis of the interposed saphenous vein segment (Fig. 3). In September, 1973, the right kidney was removed and an *ex vivo* repair was performed, again using the hypogastric artery. The patient is normotensive 6 months after surgery.

Comment. This case emphasizes the failure of an autologous saphenous vein graft for *in situ* branch renal artery replacement and the feasibility of a successful *ex vivo* repair following a failed reconstruction.

Case 2. A 46-year-old woman with congenital absence of the right kidney underwent left ureterolithotomy 8 years previously. Two months prior to admission, the patient had flank pain and hematuria. Arteriography showed a large aneurysm arising from one of the segmental branches of the left renal artery (Fig. 3). Renal function was normal. In August, 1974, the patient underwent *ex vivo* repair of her left kidney. At the time, the saccular aneurysm was totally excised and the renal artery branches were reconstructed with an arterial autograft applied as a patch. Because of previous ureteral surgery, the ureter was not detached. Following repair, the kidney was placed in its normal position and reanastomosis of the main renal artery and renal vein was ac-

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TABLE 1.

Patient Age	Duration of Hypertension	Left Kidney					Right Kidney					Date of Operation	Latest B.P.
		Disease	Repair	No. of Branches	Ureter	Graft	Disease	Repair	No. of Branches	Ureter	Graft		
N.P., 39	2 yrs	FM	EV	3	UV	hypogastric	FM	EV	2	UV	hypogastric	2/72	130/90
P.G., 43	5 yrs	FM	EV	3	UV	splenic	FM	Nephrectomy tomy	3			3/73	130/80
H.W., 42	4 yrs	FM	EV	2	UV	hypogastric	FM	IS	1	intact	saph vein	3/74	
							FM	EV	3	intact	hypogastric	11/74	114/86
D.F., 22	1 yr	FM	EV	2	UV	hypogastric			Normal			7/74	120/70
F.G., 14	1½ yrs	FM	EV	3	UV	hypogastric			Normal			8/74	120/80
E.E., 46	—	Aneurysm	EV	4	intact	hypogastric			Absent			9/74	130/90
C.H., 54	5 yrs	FM	IS	1	intact	external iliac	FM	EV	2	intact	common iliac & bifurcation	10/74	140/80
P.F., 26	1 yr			Normal			FM	EV	4	intact	hypogastric	12/74	110/70
P.B., 22	2 yrs			Normal			FM	EV	3	UV	hypogastric	1/75	118/70
M.O., 39	2 yrs			Normal			FM	EV	3	intact	hypogastric	1/75	130/80

Note: F M—Fibromuscular dysplasia; EV—*Ex-vivo* repair; IS—*In situ* repair; UV—Uretero-vesicle implantation

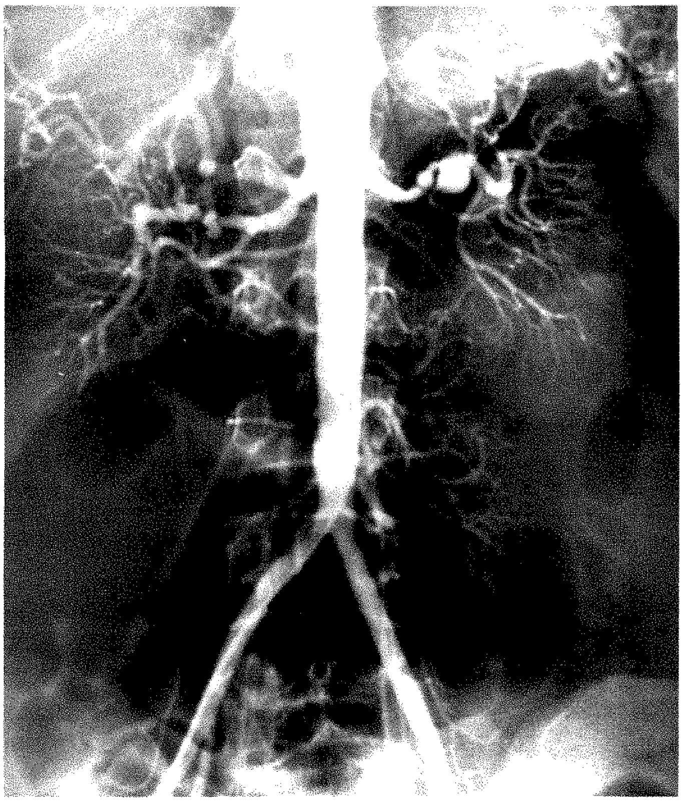

FIG. 1. Preoperative arteriogram of patient H. W. showing localized stenosis of the right renal artery distal to its first bifurcation and extensive left renal artery fibromuscular dysplasia.

complished. Postoperative arteriography showed a patent arterial repair without evidence of the aneurysm. The patient has been asymptomatic since operation (Fig. 4).

Comment. This case demonstrates a successful *ex vivo* repair for a branch renal artery aneurysm without detachment of the ureter.

Case 3. A 54-year-old woman had been hypertensive for the past 5 years. Arteriography at the time of admission showed bilateral fibromuscular dysplasia. The disease in the right renal artery involved multiple branches. On the left only the main renal artery was involved (Fig. 5). In November, 1974, the patient underwent a right *ex vivo* repair and a left *in situ* repair. The arterial autograft was obtained by resecting the left common iliac artery, the internal iliac (hypogastric) artery and the external iliac artery. Continuity of the iliac vessels was restored with an 8 mm knitted graft. The common iliac artery with its bifurcation of internal iliac (hypogastric) and external iliac arteries was used for the *ex vivo* repair on the right. The remainder of the external iliac artery was used as an aorto-renal autograft to replace the diseased left main renal artery (Fig. 6). The patient has remained normotensive since surgery.

Comment. This case demonstrates the use of two surgical teams to reconstruct bilateral disease—right, *ex vivo* and left, *in situ*.

Case 4. A 14-year-old high school student was found on routine physical examination to be hypertensive. Complete workup including renal arteriography revealed a normal right kidney but the left kidney was supplied by two arteries. The larger inferior renal artery supplying most of the left kidney appeared to be normal. There was a collateral circulation in the mid portion of the superior renal artery where a focal defect was seen. The distal portion of the renal artery was opacified via the collateral (Fig. 7). In July, 1974, the patient underwent left *ex vivo* repair. The entire diseased upper renal artery was excised and reconstruction was performed using the patient's hypogastric artery (Fig. 8).

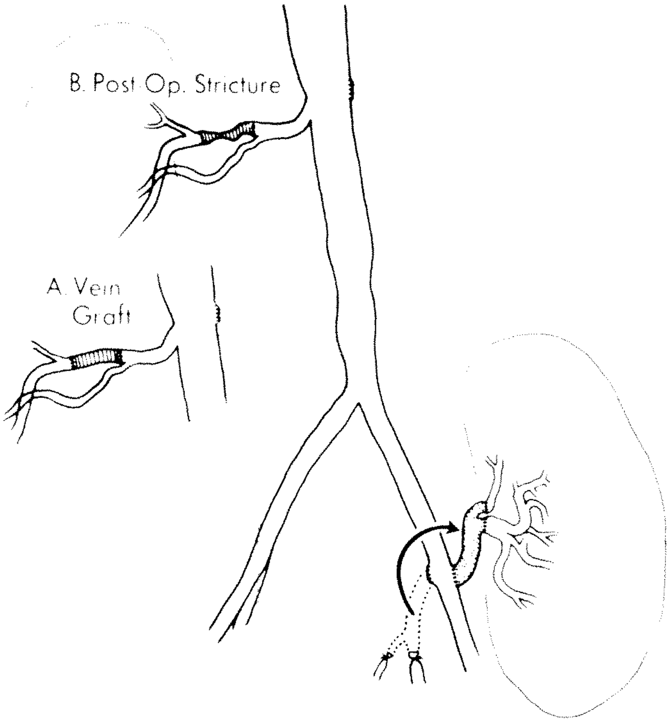

FIG. 2. Schematic drawing of the first arterial repair, patient H.W.

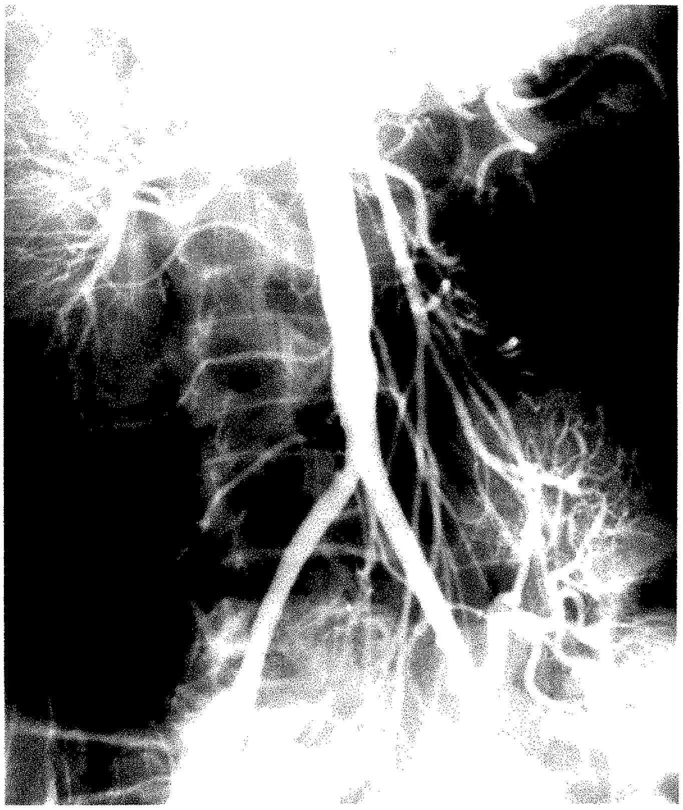

FIG. 3. Arteriogram of patient H.W. prior to second repair showing stenosis of interposed saphenous vein graft of the right kidney. The left autotransplanted kidney now has a normal arterial supply.

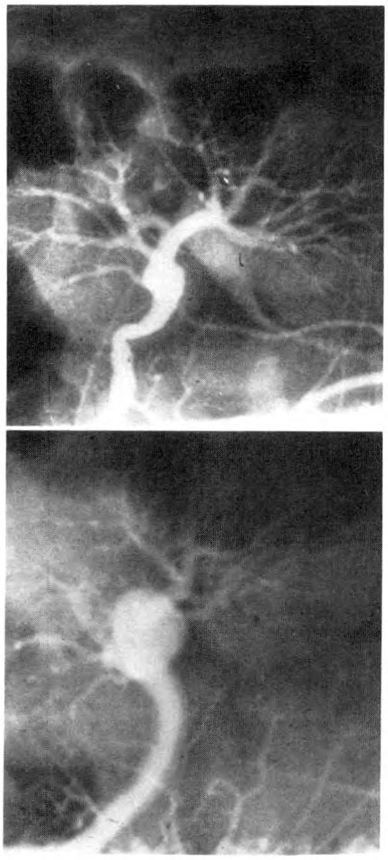

FIG. 4. Pre and postoperative arteriogram on patient E. E. showing the renal artery aneurysm and postoperative repair.

Subsequent examination of the upper polar artery revealed a septum completely obstructing flow to the upper pole of the left kidney. This area was supplied by collateral circulation only. The patient has remained normotensive since surgery.

Comment. This case demonstrates a successful *ex vivo* reconstruction in a child where renal preservation is critical.

Case 5. A 22-year-old woman was found to be hypertensive one year prior to admission. Her symptoms progressed in the 5 months prior to admission. Renal arteriography showed atrophy of the right kidney secondary to severe fibromuscular dysplasia. Total renal function was normal. Although the right kidney was atrophied, nephrectomy was not advised because of her age and the possibility of subsequent disease of her left kidney. A right *ex vivo* repair was performed using the hypogastric artery (Fig. 9). She has remained normotensive since her operation in January, 1975.

Comment. This case demonstrates that renal atrophy unless severe is no contraindication to *ex vivo* surgical repair.

Discussion

Renal autotransplantation was first described by Hardy in 1963[9] and was first successfully performed for renovascular hypertension by Woodruff in 1964.[18] Oda first reported nephrectomy with *ex vivo* microvascular reconstruction and successful autoimplantation in 1967.[15] In 1970, we described a technique of reconstruction of renal artery branches in laboratory animals using continuous extracorporeal hypothermic perfusion.[1] Cormal et al. were the first to report the clinical use of this technique.[5] In the last 5 years, many case reports or nephrectomy and *ex vivo* repair using either hypothermic perfusion of hypothermia alone have been published.[3,7,8,11,12]

Ex vivo surgery should be considered only when *in situ* surgical repair is deemed impossible. Extension of the disease to the primary renal artery branches does not necessarily preclude *in situ* repair. If the branches are 3 mm or more in diameter, *in situ* bifurcation reconstruc-

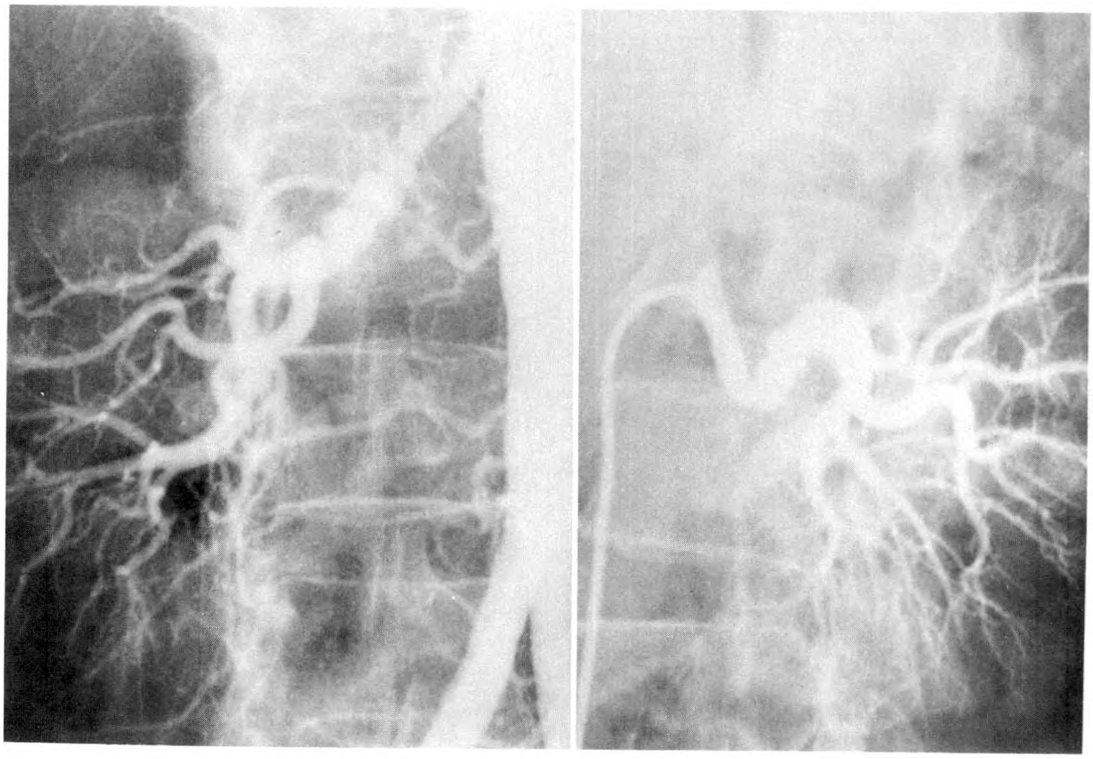

FIG. 5. Preoperative arteriograms on patient C. H. Note the short segment of patent renal artery proximal to the first bifurcation in the left kidney.

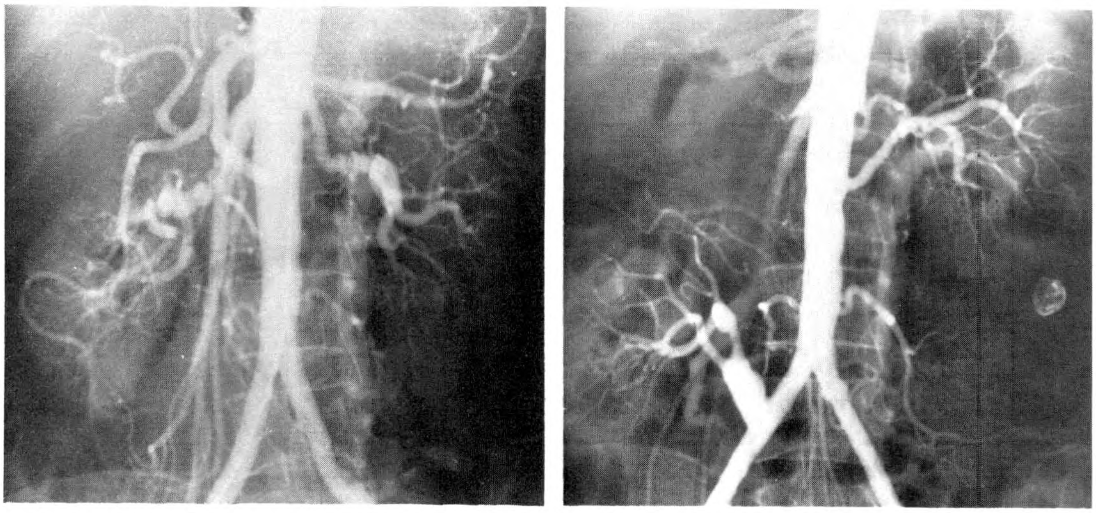

FIG. 6. Preoperative left and postoperative right arteriograms on patient C. H. showing patent *ex vivo* repair of the right kidney and patent *in situ* repair of the left kidney.

tion can be performed with relative ease. As suggested by Fry and others, minimal stenosis of branch arteries, especially if not associated with aneurysm, can be successfully dilated.[6]

In this report, arterial autografts were used for arterial reconstruction, rather than autologous saphenous vein grafts. In two recent publications the longterm fate of autologous saphenous veins used in aorto-renal bypass procedures was reported.[4,17] An alarming 40 to 60% incidence of graft abnormality, including thrombosis, dilatation, aneurysm formation or stenosis was found. However, the hypogastric artery has been used in thousands of renal transplant procedures with only suture line stenosis being observed. Furthermore, a recent survey of aorto-renal arterial autografts performed for renovascular hypertension at the University of California Medical Center in San Francisco showed none of these complications during a 10-year follow up period.[13]

Ex vivo repair can be performed by both continuous

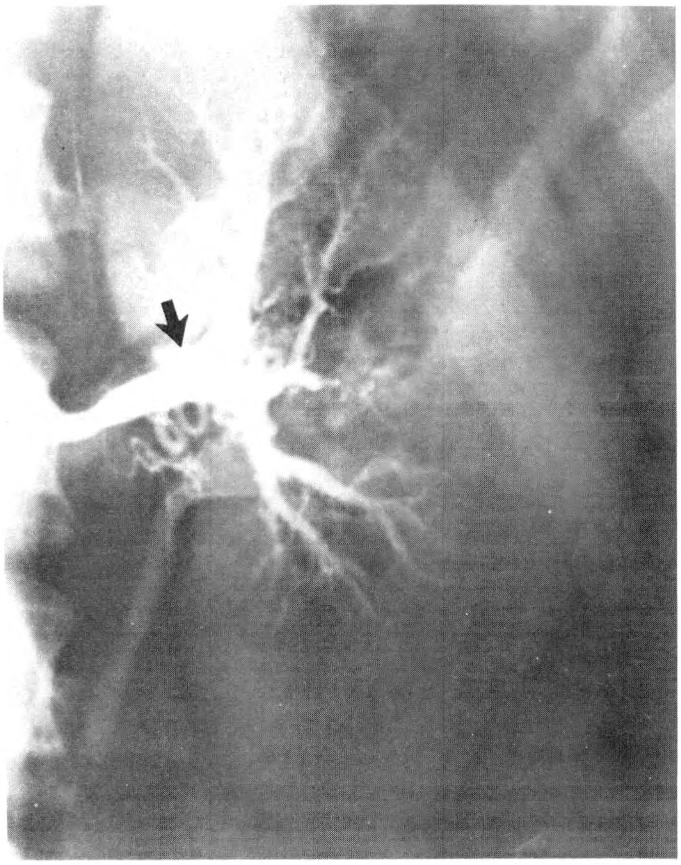

FIG. 7. Schematic drawing of dissecting platform and perfusion circuit.

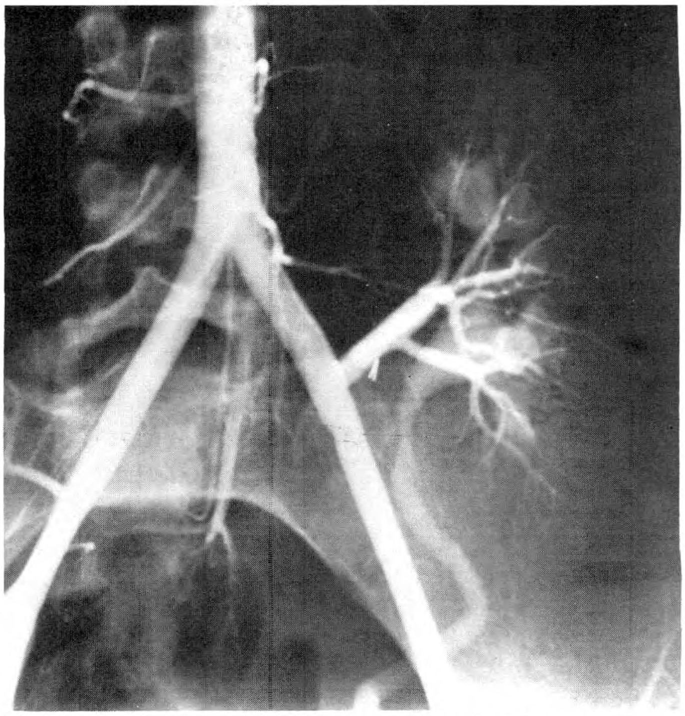

FIG. 8. Postoperative arteriogram on patient S. G. The normal lower polar artery was anastomosed end-to-side to the interposed hypogastric artery.

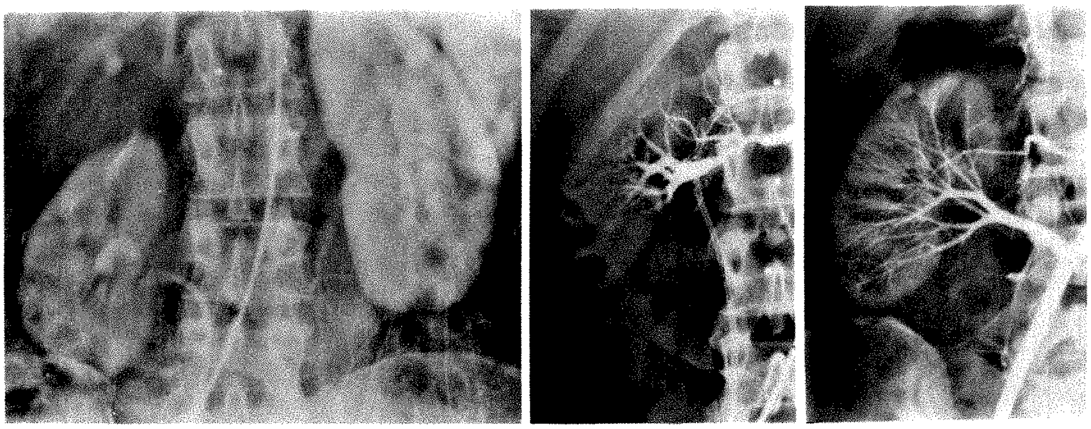

FIG. 9. Preoperative arteriogram on patient P. B. showing moderate atrophy of the right kidney and severe fibromuscular dysplasia of the right renal artery. The postoperative *ex vivo* repair is shown on the right.

hypothermic perfusion and simple cold storage. Three of the kidneys in this series were reconstructed using hypothermia alone and 8 were reconstructed during continuous hypothermic perfusion. The advantages of continuous perfusion are: (1) Dissection of the renal branches is easier as these vessels are distended. (2) Continued perfusion allows extra protection for the kidney even when the procedure is lengthy. (3) Following reconstruction, perfusion pressure can be set at systolic levels and small anastomotic leaks can be closed prior to autotransplantation. Bleeding after autotransplantation from unrecognized anastomotic leaks requires additional sutures *in situ*. This may be hazardous, especially if the bleeding site is a small vessel anastomosis in the renal hilum. When hypothermia alone is used, cold Ringer's lactate is an effective solution. There is no evidence that for the short period of time required for repair, hyperosmolar solutions provide greater protection than hypothermia with cold Ringer's lactate solution.[10]

Management of the ureter appears to be relatively unimportant. The ureter can be left intact during the reconstruction as long as retrograde bleeding into the kidney and/or perfusion is prevented by temporary occlusion of the ureter with a soft elastic tubing. Redundancy of the ureter appears to be no problem if the ureter is left intact and the kidney is reimplanted lower in the abdomen. However, if the surgeon is completely familiar with the techniques of renal transplantation, ureterovesicle implantation should have a complication rate of less than 0.5 per cent.[16] When one kidney only is being reconstructed, it is simple to leave the ureter intact and perform the reconstruction on a specially constructed platform placed on the patient's lower abdomen (Fig. 10). For bilateral reconstruction, detachment of the ureter allows complete removal of one kidney from the abdomen and permits a second team to work on the contralateral kidney *in situ* while the first kidney is reconstructed at an adjacent dissecting platform. As bilateral reconstructions can be lengthy, the use of two surgical teams can shorten the operative period.

Arteriography following *ex vivo* repair has been advised by some authors prior to replantation of the kidney.[5] Although our dissecting platform permits *ex vivo* arteriography, we have not used this technique because of the possible side effects and toxicities of the contrast medium. Usually the status of the disease has been accurately identified by preoperative selective arteriography. Following reconstruction, simple calibration with the commercially available dilators used for Scribner shunts, are useful to assess patency of anastomosis. If a contrast medium is used during or following the *ex vivo* repair it should not be recirculated and should be washed out of the kidney.

The decision whether a kidney should be repaired *in situ* or *ex vivo* should be made prior to surgery. Acting according to the concept that *in situ* repair should be attempted first and if it proves to be impossible then the kidney should be repaired *ex vivo* will probably give poor results. *Ex vivo* repair requires complete mobilization of the kidney. This requires additional time and is usually not done for *in situ* repair. Furthermore, the warm ischemia which occurs during an unsuccessful *in situ* repair may make the organ unsuitable for subsequent *ex vivo* repair.

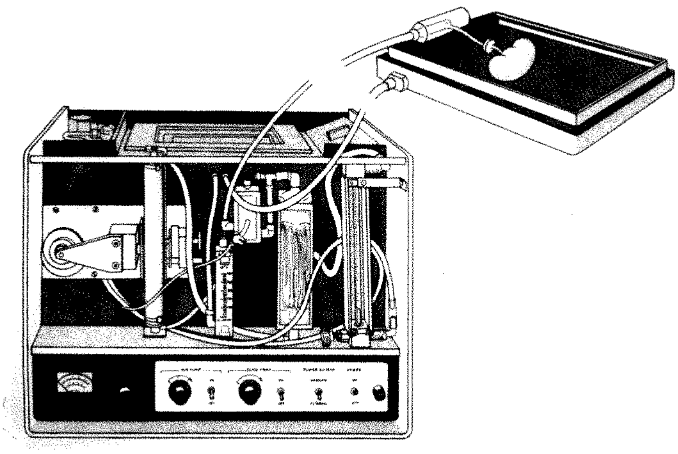

FIG. 10.

The kidney should be removed under optimum conditions. This includes the use of mannitol and careful dissection so that vasospasm does not occur during the nephrectomy with tubular necrosis as a sequellae later.[14] Tubular necrosis causes reduced renal blood flow after reimplantation and thus increased the likelihood of thrombosis, especially if the repair involves multiple small vessels. The anastomosis should be done with fine sutures (6-0 or 7-0 Tycron is used). In young women we have reimplanted the kidney high on the iliac vein and iliac artery. This avoids a pelvic location of the kidney, whould there be subsequent pregnancies.

The indications for *ex vivo* reconstruction should be tailored to the individual patient's needs but in general are the following: 1) Failure of medical means to control hypertension, progression of the arterial lesions or decrease in renal function. 2) Lesions which are uncorrectable by *in situ* vascular reconstructive procedures. 3) Bilateral disease or unilateral disease in a single kidney, thus precluding nephrectomy. 4) Unilateral disease with a normal contralateral kidney in patients under 40 years of age. 5) Previously unsuccessful *in situ* repair (If the first reconstruction has failed due to a technical error, a second *in situ* reconstruction may be possible.) Extensive scarring from the previous procedure might make a second *in situ* procedure extremely difficult and *ex vivo* repair may be a safer alternative. Nephrectomy rather than *ex vivo* reconstruction is indicated for: 1) Unilateral disease in an elderly patient where the chance of recurrence of fibromuscular dysplasia in the normal kidney is unlikely or 2) Severe atrophy of the affected kidney which would be unimportant to preserve.

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DISCUSSION

DR. THOMAS E. STARZL (Denver, Colorado): It has been obvious almost from the moment of its introduction that the preservation techniques of Belzer would revolutionize the practice of renal transplantation. It is also clear that non-transplant urologic practices and vascular surgical approaches may be affected as well, as Dr. Stoney has shown us so beautifully today. Drs. Stoney and Belzer have concentrated on the difficult renal vascular reconstructions which have also provided us with our main published experience now comprising 14 cases involving 18 kidneys.

(Slide) There are other indications than vascular lesions for the so-called bench work surgery, as Russ Scott has called it, including otherwise inoperable stone disease. This man had a staghorn calculus in his only kidney. The kidney was removed, bivalved while on the Belzer machine, cleaned out, and autotransplanted to the location seen here.

(Slide) This woman had a large carcinoma involving the lower two-thirds of her only kidney. She was treated in the same general way with protection of the kidney on the Belzer machine and reconstruction and autotransplantation of this rather small remnant. She has no evidence of recurrence now after more than a year.

We have also used autotransplantation to allow short ureters to be reimplanted into the bladder as was first described by James Hardy in 1963, and to protect kidneys on the Belzer machine while diffuse aneurysms of the abdominal aorta involving the renal blood supply have been excised and replaced.

Dr. Stoney's work has shown us how technological advancements in one area of surgery can advance the level of performance in other disciplines. This is a lesson that was eloquently stated by those great plastic surgeons, Milt Edgerton and Joe Murray, on Wednesday night, in their papers on facial deformities. No better example of this principle could be cited than Drs. Stoney and Belzer's brilliant work.

PROFESSOR LARS-ERIK GELIN (Göteborg, Sweden): In relation to Dr. Stoney's beautiful presentation, I should like to report on our series of patients undergoing extracorporeal kidney surgery and illustrate the usefulness of the extracorporeal method with one special case.

Since 1968, we have treated 36 kidneys in 33 patients on the following indications: Tumors in a single kidney, bilateral kidney tumors, renal artery aneurysms and distal renal artery stenosis, coralloid stones in single kidneys and two cases with aortic aneurysm involving the renal arteries and the special case I'll come to presently.

The outcome of the repairs for distal renal artery stenosis producing severe hypertension appears on this slide. All patients except one became normotensive after the construction.

(Slide) This will evidence the outcome of repair of distal renal artery aneurysm in nine kidneys and it's confirmed that these kidneys have excellent function after the repair.

The great advantages with the extracorporeal method to approach difficult technical problems, evidenced by both Dr. Stoney and Dr. Starzl, may perhaps be best illustrated by the following case.

(Slide) A woman who presented herself at the age of 50 with progressive heart trouble, a machinery murmur over the back, slight hypertension, and periods of hematuria.

The angiogram demonstrated two renal arteries on the left side. The injection made in the superior artery filled immediately the lower one. There was a filling of a huge arterial-venous fistula system into a lake—a venous lake. This very rare condition has been previously described, but as far as we know not conservatively treated before.

At exploration the renal vein was very huge and didn't allow proper insight to the arterial anatomy. The kidney was therefore removed.

We cooled it simply with a 5% Rheomacrodex solution and put it on a portion of ice on a side table. It then became evident after careful dissection that there were four direct arterio-arterio and arterio-venous connections and a huge venous lake seen below as a red tumor.

As the dissection went on, the lake became more apparent; and, the renal aneurysms seen with a direct connection with the lake.

Removal of these vascular anastomotic portions was done and then reconstruction with the use of saphenous veins for six separate arterial anastomoses.

After reimplantation, this kidney had immediate function as all kidneys have had. The angiogram at followup demonstrated still an overlooked arterio-venous connection which we tried to preserve in order to save that very tiny, small artery nourishing the distal pole of the kidney.

Concerning the method of preservation, I don't find continuous perfusion necessary. It will complicate the procedure unnecessarily and remove some of the advantages of the extracorporeal method. Its simplicity is here one key to the success as to the usefulness of the method in any operating theatre. Extracorporeal kidney surgery requires only equipment available in any operating theatre and it is a safe method.

Concerning the nomenclature for this kind of surgery, I think the term extracorporeal surgery is more adequate than the term used by Stoney and Belzer. Ex vivo is misleading. It is indeed a method which relies on viability.

DR. JOHN H. FOSTER (Nashville, Tennessee): At Vanderbilt we have a modest experience with this type of procedure. Working with Dr. Robert Richie, chief of our renal transplant team, we have followup studies on four extracorporeal renal artery reconstructions in three patients.

One patient, a 55-year-old man with severe hypertension and bilateral fibromuscular dysplasia with aneurysms involving the branch renal arteries, underwent bilateral two-stage (three-week interval) ex vivo reconstruction in 1972. The kidneys were perfused with the Belzer pump during the reconstructions in which the branch renal arteries were implanted into a segment of saphenous vein. The ureters were not divided. After division of the renal artery and vein, the mobilized kidney was brought out onto the abdominal wall for the reconstruction. Following the reconstruction, the vein graft and renal vein were implanted into the iliac artery and vena cava or iliac vein. The lower pole of the left kidney was found to be infarcted and was resected. Thus three branch arteries were anastomosed to the vein graft on the right and two branch arteries anastomosed to the vein graft on the left. One large branch on the left supplied most of the remaining kidney. This aortogram, obtained six months later, showed good configuration of the vein grafts and patency of all the anastomoses. A recent aortogram, 30 months postoperatively, shows the small branch artery on the left is occluded; all other anastomoses are patent and the vein grafts have maintained a normal caliber and configuration. The patient, who remained hypertensive after the repair on the right side, has been normotensive without medication during the 30 months following the second operation and remains so despite the small branch artery occlusion.

In our other two patients, followup arteriographic studies have shown a good result in one and recurrent hypertension with multiple intrarenal branch artery stenoses in the other.

We believe it is very important to obtain careful followup arteriographic studies in these patients in order to evaluate the long term fate of extracorporeal renal arterial reconstructions. This technic is a valuable addition to our armamentarium which will allow renal arterial reconstruction rather than nephrectomy in some patients with extensive and severe branch artery fibrodysplastic lesions. However a word of caution is in order, the technic is not sufficiently established to be applied in all cases with occlusive lesions of the distal third of the main renal artery. Most of these can be reconstructed using the more conventional and simpler in-situ technics which have been subjected to careful followup arteriographic studies.

I would like to ask Dr. Stoney to comment on the relative merits of continuous perfusion versus simple cooling of the kidney in ex vivo repair of the renal artery. The latter technic which is less complicated, less time consuming and yet effective in preserving the kidney would seem to be preferable.

DR. WILLARD E. GOODWIN (Los Angeles): As a historical point, I'd like to say that the term "work bench surgery" certainly was first coined and used by Michael Woodruff in Edinburgh, more than 15 years ago.

In our experience at U.C.L.A., perfusion is not necessary with a pump. We use "sacks' solution," for cold perfusion, and we get just as good preservation by gravity flow without a pump.

We're hearing many papers on this subject at the urological meetings throughout the country. After an initial wave of great enthusiasm, it became clear that some surgeons were doing "work bench surgery" as a tour de force in some cases when they might just as well have done it in situ.

I think one of the rules ought to be not to do this unless there's no other way to do it.

Obviously, we saw some cases today where it was the only way.

The other thing I think is important is to emphasize that it's all right to divide the ureter if necessary, but if it's not necessary, there's great advantage to leaving it intact.

DR. RONALD J. STONEY (Closing discussion): Dr. Starzl, we agree with you that there are clearly other indications for the use of extracorporeal ex vivo repairs of the kidney. We used this technique to repair injuries of the ureter, as well as tumor and stone disease. I think your remarks clearly extend the obvious potential of this technique.

Dr. Gelin, we're indebted to you for your long interest in this problem of bloodless surgery. Your repairs for renal artery stenosis were impressive to me. However, I am concerned about the late behavior of the saphenous vein as a renal artery graft, since we've had two rather alarming reports recently describing degenerative changes in the vein grafts.

Your case of the repair of a renal AV malformation is intriguing. Prior to the development of this technique in our hospital, we removed the kidney of a hypertensive four-year-old child for nearly an identical lesion. Using the ex vivo techniques in this child I could have saved his kidney.

I agree, Dr. Gelin, that you don't need continuous perfusion. In fact, a number of these cases were performed with simple temporary cold storage as has been alluded by other discussants. I think one advantage of perfusion is to examine the reconstruction just prior to replantation of the kidney. It is difficult to repair small leaks in vessels of one or two millimeters in the hylus of the kidney following replantation, and this difficulty is avoided by detecting the leak and repairing it during perfusion.

Cold storage is adequate for renal preservation during most reconstructions.

I agree with Dr. Foster that the long term assessment of these microvascular branch artery reconstructions is imperative, and he has pointed this out in his work over the years. We will continue to follow these patients with serial angiograms as we do patients with main renal artery reconstructions.

Dr. Goodwin, we agree that if you can leave the ureter intact and perform the repair adequately you should. In this series, we have performed four repairs without ureter division by placing the kidney on the abdominal wall for reconstruction.

Myeloproliferative Disorders

SEYMOUR I. SCHWARTZ, M.D.*

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Forty-three operative procedures were performed on a population of 250 patients with myeloproliferative disorders, including polycythemia vera, myeloid metaplasia (MM) and chronic myelogenous leukemia (CML). The overall operative mortality was approximately 7% and the incidence of excessive bleeding which could be related to coagulopathy was 5%. Twenty-one patients with MM or CML underwent splenectomy for palliation of symptoms related to the enlarged spleen or hematologic problems. Eighty-four percent of the latter group were improved. Adverse hematologic effects which could be attributed to splenectomy in these patients were confined to two patients who developed marked thrombocytosis. Among the 23 patients with MM, 9 had portal hypertension. Three underwent portacaval shunt and one a splenorenal shunt for bleeding varices. One of the patients died of hepatic necrosis. Estimated hepatic blood flow determinations (EHBF) in 4 patients with portal hypertension demonstrated a marked absolute increase and an increase in the ratio of EHBF/Cardiac Index. Absence of any evidence of intrahepatic or extrahepatic obstruction in these patients and the demonstration that splenectomy relieved portal hypertension defined at surgery in 4 patients, suggests that augmented adhepatic flow contributes to portal hypertension in some cases. The review leads to the conclusions that: 1) Operative procedures in prepared patients with myeloproliferative disorders are not associated with prohibitive mortality and morbidity rates. 2) Splenectomy is indicated for patients with increasing transfusion requirements and symptomatic splenomegaly or hypersplenism and should be performed early in the course of disease. 3) When associated portal hypertension and bleeding varices are present, hemodynamic studies should be carried out to define if splenectomy alone, or a portal systemic decompressive procedure is indicated.

THE MYELOPROLIFERATIVE DISORDERS include a spectrum of diseases, each of which may be due to a different disturbance in proliferation and/or maturation of the hematopoietic stem cell of marrow. Polycythemia Vera (PV), Acute and Chronic Myelogenous Leukemia (AML and CML), Myeloid Metaplasia (Myelofibrosis, Myelosclerosis) (MM) and Essential Thrombocythemia all have been included within the general category of myeloproliferative disorders. Surgical consideration of patients with myeloproliferative disorders relates to: 1) a general appreciation of the operative risk for any surgical procedure in these patients; 2) the application of splenectomy as a palliative procedure in patients with MM and CML; and 3) the management of portal hypertension and variceal bleeding in patients with MM.

Material and Methods

The records of 250 patients with myeloproliferative disorders seen at the Strong Memorial Hospital between 1955 and 1974 were reviewed. Included were 90 patients with PV, 64 patients with MM and 96 patients with CML. Some of these patients have progressed from PV to MM. Each patient was assigned to the more advanced category, unless an operative procedure was performed, in which case he or she was considered in that category during which the operation was carried out. All patients had the diagnosis established by blood counts, peripheral blood smears, bone marrow aspirates or biopsies. In patients subjected to splenectomy and/or portal decompressive procedures, histologic evaluation of the spleen and/or liver contributed to the diagnosis.

Operative mortality was considered as that occurring during the hospitalization for the procedure or within 30 days. Excessive bleeding related to an hemostatic defect was defined as that associated with a 5% reduction in

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hematocrit, requirement for a number of transfusions significantly greater than that usually associated with the procedure, reexploration at which a single bleeding site could not be defined, or a combination of the above.

Portal pressures were measured during the operative procedure in either the portal vein itself, or in an omental vein with the portal vein as a reference level, using a spinal manometer filled with saline. Central venous pressures (CVP) were determined simultaneously.

Hemodynamic studies were performed on awake patients who were not premedicated. Hepatic blood flow (EHBF) during the postabsorptive state was carried out according to the method of Leevy et al.[12] employing indocyanine green dye. Pressure measurements in these patients were made using Statham P-23 AA strain gauges and a Sanborn direct writing recorder. Cardiac output determinations were made from the standard indocyanine green indicator dilution curves. Body surface area estimates were derived from a Du Bois normogram.

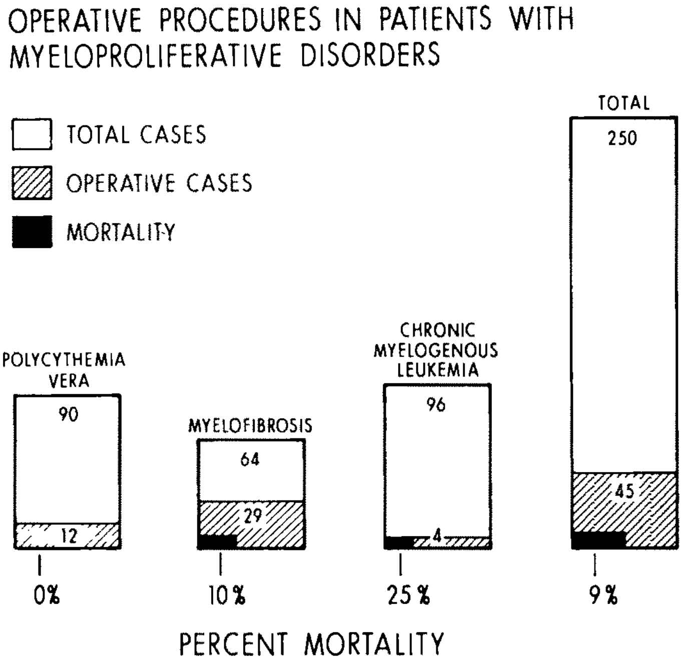

FIG. 1. Mortality Associated with Operative Procedures in patients with Myeloproliferative Disorders.

Results

I. Operative procedures in all categories

Forty-five operative procedures were performed in 41 patients. Twelve procedures were carried out in patients with PV, 29 were performed in patients with MM, and four procedures were performed in patients with CML (Table I). There were 4 deaths related to the operative procedure, resulting in an overall mortality rate of 9%. None of the patients with PV died; one of the patients with CML died, while in the group with MM, the mortality rate was 10% (Fig. 1).

In the MM group, a patient died following splenectomy with ensuing subphrenic abscess and sepsis. Another patient died due to hepatic necrosis following an end-to-side portacaval anastomosis. The third death in the MM group occurred in a 48-year-old woman who had a 4,950 gram spleen removed because of symptomatic splenomegaly on 5-18-72 without intraoperative or postoperative transfusional requirement. On 2-28-73 she underwent transthoracic subclavian endarterectomy. Her preoperative hematocrit was 35, WBC 50,000 and platelets 160,000/mm.^{3} Postoperatively she developed an hemothorax which required three reexplorations. She subsequently developed aspiration pneumonia, respiratory failure and died 6 weeks after the first thoracotomy. One patient who underwent splenectomy for hypersplenism associated with CML died following discharge but within one month of surgery. At autopsy there were extensive thromboses of the renal veins and mesenteric veins.

In the group of patients with PV, there was no excessive bleeding, and only one significant postoperative infection; a subphrenic abscess following cholecystectomy for acute cholecystitis. In one of the patients, the preoperative platelet count was 843,000/mm^3 while in all others this was in the normal range. One patient was

TABLE 1. *Operative Procedures in Patients With Myeloproliferative Disorders*

PV		MM		CML	
Arterial Reconstructions	3	Splenectomy	22 (1*, 1+)	Splenectomy	3 (1+)
Amputations	2	(With Splenorenal shunt 1)		Vagotomy & Antrectomy	1
Lumbar Sympathectomy		Portacaval Shunt	3 (1+)		
Aortic Valve Replacement		Subclavian Endarterectomy	1 (1+)		
Pericardial Poudrage		Cholecystectomy			
Nephrectomy		Vagotomy & Pyloroplasty			
Mastectomy		Hernia Repair			
Drainage Subphrenic Abscess					
Cholecystectomy					
Total:	12	Total:	29	Total:	4
Deaths:	0	Deaths:	3	Deaths:	1

*Excessive bleeding
+Death

TABLE 2. *Indications for Splenectomy/Effects*

	Primary	Improvement In Survivors	Secondary	Improvement In Survivors
Symptomatic Splenomegaly/ Hypermetabolism	8 (2+)	6/6	—	—
Anemia/ Hemolysis	10	7/10	6	5/6
Thrombocytopenia	4	3/4	8	7/8
Leukopenia	2	2/2	—	—
Total:	24	19/22 (86%)		12/14 (86%)

+Death

operated on with a hematocrit of 63, while in the remainder the hematocrit was less than 52%. Ten of the 12 patients had been treated with busulfan, ^{32}P, multiple phlebotomies or a combination of these modalities. In the 6 patients requiring an operation for peripheral arterial disease, neither hematocrit nor platelet count were significantly increased.

Among the 27 patients with MM undergoing 29 procedures, excessive bleeding occurred in 3 cases; in the subclavian endarterectomy described above and in two of the 21 splenectomies. In none of these three could the bleeding be attributed to a specific bleeding site, and none of these patients had platelet counts less than 70,000/mm.^{3} In both splenectomy cases, reexploration and evacuation of the clot from the left subphrenic space resulted in cessation of bleeding. There was no excessive bleeding in the two patients with platelet counts greater than 350,000/mm.^{3} At the operative procedure in patients with MM, no patient had a hematocrit greater than 52. Two of the three deaths in the group of patients with MM were related to sepsis.

The three splenectomies in the CML group were performed in patients with mild anemia; two had thrombocytopenia, and one mild thrombocytosis. There were no immediate postoperative complications, but one patient had a slightly elevated platelet count and died within a month of surgery from extensive visceral venous thromboses and a blastic crisis.

II. Splenectomy as a Palliative Procedure

Twenty-four splenectomies were performed as palliative procedures in patients with MM or CML. The indications are listed in Table 2. In 8 patients the major indication was symptomatic splenomegaly in which the spleen was of such magnitude as to be uncomfortable or to interfere with alimentation, or in which multiple episodes of painful splenic infarcts occurred. In some patients there was associated hypermetabolism. In 10 patients, a significantly increased transfusion requirement or hemolysis was the major indication, while in 4 patients thrombocytopenia with clinical manifestations constituted the major indication. In two patients leukopenia interfering with the defense mechanism toward an infection, prompted splenectomy. All patients had received medical therapy, usually from months to years prior to the operation. The regimen varied and consisted of phlebotomies, prednisone, ^{32}P, busulfan, cyclophosphamide or a combination of these.

The mean weight of the spleens which were removed for symptomatic splenomegaly was about 3,150 gm, range of 2,250-7,650 gm. There were two patients with an accessory spleen. Five of the patients had platelet counts of 70,000/mm^3 or less. The left subphrenic space was drained in 7 patients. Reexploration for continued bleeding was required in 2 patients, one of whom had thrombocytopenia, and one was a patient in whom the space was not drained. One of the patients developed a subphrenic abscess and died of sepsis a month after the second procedure. The other death occurred in the patient with CML described above. The 6 remaining patients had symptomatic improvement, and in no instance was there an adverse hematologic effect, i.e., more profound anemia, thrombocytopenia or leukopenia. Two of the patients have died, years after the operative procedure for CML.

In 16 patients, the major indication was hypersplenism, with anemia, thrombocytopenia or leukopenia the factor prompting the operative procedure (Table 2). The mean weight of the spleens in these patients was 2,250 gm (range 675 gm-3,150 gm). There were three patients in whom small, accessory spleens were also removed. The subphrenic space was drained in 14 patients.

The hematologic defect which constituted the prime indication for surgery was improved in 12 patients for an overall therapeutic effect of 75% (Fig. 2). Seven of the 10 patients with an increase in transfusion requirements had this significantly reduced for months to years following splenectomy. Five of the 6 patients in whom anemia was a contributory factor, had some increase in the hematocrit following splenectomy. Three of the 4 patients with symptomatic thrombocytopenia as the major factor, improved following splenectomy. Platelets were not ad-

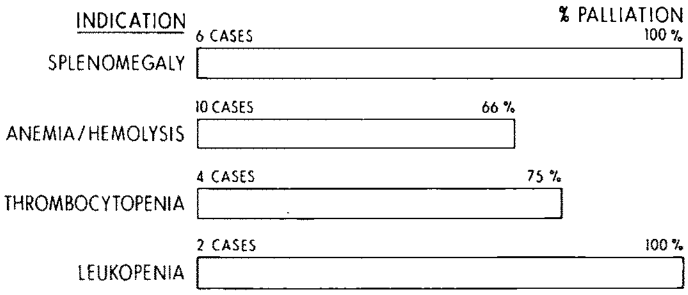

FIG. 2. Results with Splenectomy in Patients with Myeloproliferative Disorders.

ministered preoperatively in these patients but 10 to 20 packs were given intraoperatively to 2 of the patients following splenectomy. In one of these, there was significant postoperative bleeding requiring evacuation of a hematoma, but the platelet count increased significantly from 1,000/mm^3 to 60,000/mm^3 the week after surgery and was maintained above 70,000/mm^3 for 5 years. The patient in whom no improvement occurred, has a platelet count which has persisted at 18,000/mm^3 and has had no bleeding since surgery for the past 4 years. In the 8 patients with thrombocytopenia as a contributory factor, an increase in the count of at least 20,000/mm^3 has been maintained in 7 patients since splenectomy.

The two patients subjected to splenectomy for uncontrollable pulmonary infection related to white blood counts of 800/mm^3 and 1200/mm^3, had spleen weights of 675 gm and 1,350 gm respectively. There were no accessory spleens. In both instances, the infection came under control postoperatively with continuance of preoperative antibiotic therapy which had previously been ineffective. In one patient, the initial increase in white blood count was minimal, i.e., 800/mm^3 to 1600/mm^3, and the white blood count has been sustained at about 3,000/mm^3 with no subsequent infections for the past month. In the second patient, the white blood count increased to 6,000/mm^3 and has been maintained for 6 months at that level without evidence of further infection.

There were two significant postoperative infections; both subphrenic abscesses. One of these patients died of uncontrollable sepsis. The other developed gram negative sepsis due to *Serratia marcescens* following drainage of an infected subphrenic hematoma. This responded to gentamycin and the patient did well for 4½ years. There was no instance of worsening of the hematologic profile subsequent to splenectomy in *any* patients who underwent splenectomy for palliation. The WBC increased in the immediate postoperative period in 84% of the patients. In 11 there was marked leukocytosis preoperatively, and this persisted postoperatively. In two patients there were platelet counts of 480,000/mm^3 and 380,000/mm^3 preoperatively. In the former, the count increased temporarily to 843,000/mm^3 with no adverse effects. The one death which may have been related to thrombocytosis occurred one month after surgery in a patient with CML. His maximum platelet count was 420,000/mm^3, but at autopsy there were thromboses and multiple mesenteric and renal veins.

Three of the patients with MM and one of the CML patients have died of their disease 3 to 7 years following splenectomy. In two of these, infection, in one a case of *Cryptococcus neoformans*, contributed to the demise.

III. Myeloid Metaplasia and Portal Hypertension

Four patients with MM underwent decompressive procedures for portal hypertension, esophagogastric varices and a history of recurrent upper gastrointestinal bleeding (Table 3). One 60-year-old woman who had been treated for pernicious anemia at age 38 and who had been diagnosed at age 50 as having MM, underwent splenectomy and splenorenal anastomosis in 1966. In the 10 antecedent years she had had multiple phlebotomies, splenic irradiation and several courses of busulfan. At surgery the liver biopsy revealed portal cirrhosis in addition to minor foci of extramedullary hematopoiesis. Since splenectomy alone affected only a minor reduction in portal pressure, a splenorenal shunt was carried out and the blood pressure reduced to near caval pressure. Her three year postoperative course was complicated by several episodes of encephalopathy which responded to protein restriction and neomycin. She died of pneumonia, and at autopsy there was no evidence of varices.

TABLE 3. *Portal Decompressive Procedures In Patients With Myeloid Metaplasia*

Procedure	Sex, Age	Cirrhosis	Result
Splenorenal Shunt	F, 60	+	Died 3 years later—pneumonia Mild recurrent encephalopathy
End-to-Side Portacaval shunt	F, 41	−	Died 36 hours later Massive hepatic necrosis
″	M, 77	+	Died 6 years later—M.I. Mild Recurrent encephalopathy
″	F, 74	−	Died 3 years later—? Etiology Mild recurrent encephalopathy

In the group subjected to end-to-side portacaval shunts, one patient developed hepatorenal failure due to massive hepatic necrosis, and died on the second postoperative day. In addition to the acute necrosis, the liver revealed foci of extramedullary hematopoiesis but no cirrhosis. The second patient, a 77-year-old man, had no recurrent bleeding post shunt, but did experience mild recurrent encephalopathy and died from cardiac problems 6 years subsequent to his shunting procedure. At the operative procedure, his liver demonstrated both extramedullary hematopoiesis and cirrhosis. The remaining patient who received an end-to-side portacaval shunt for bleeding varices was the subject of a previous case report.[16] She survived two years and her course was complicated by several episodes of mild recurrent encephalopathy. This 74-year-old woman had portal hypertension, bleeding varices and no evidence of cirrhosis or regenerative nodules. Small foci of extramedullary hematopoiesis were present in the liver. The presence of portal hypertension unassociated with any hepatic lesion which could be indicted as a cause of outflow obstruction, led to a consideration of increased flow through the splenoportal system as a factor in the production of portal

TABLE 4. *Correlation of Intraoperative Pressures (MM Patients With Suspected Portal Hypertension)*

Patient	Ascites	Varices	Portal Pressure (mm saline) Before Splenectomy	After Splenectomy	CVP	Cirrhosis	Spleen Weight (gm.)
1	+	–	110	—	—	—	1840
2	–	+	370	140	80	—	3850
3	+	–	170	—	—	—	—
4	–	+	270	110	90	–	3630
5	±	+	360	130	110	+	2200
6	–	+	480	120	80	–	4950
7	+	+	390	320	70	+	2250
8	+	+	320	290	90	+	3150

hypertension in the patient with MM and associated marked splenomegaly.

In 8 patients with MM in whom portal hypertension was anticipated due to the presence of varices or ascites, portal pressures were determined at the operative procedure, before and after splenectomy (Table 4). Two patients revealed normal pressures in the portal system, while in 6 an elevation was demonstrated. In 4 of the 6 patients, splenectomy effected a marked reduction in portal pressure to levels within the range of normal but still slightly elevated in reference to CVP. All 4 of these patients showed only small foci of extramedullary hematopoiesis in the liver, and there was no evidence of cirrhosis. In two of these patients, the varices gradually disappeared months after splenectomy. Two patients with significant cirrhosis experienced only a slight reduction in portal pressure associated with splenectomy. One of these was subjected to a concomitant splenorenal shunt.

The findings of hemodynamic studies in 4 patients with MM and suspected portal hypertension are shown in Table 5. The hepatic venous wedge pressure was greater than normal in all patients and more than twice normal in two. Similarly, the EHBF was significantly increased in all patients and more than twice normal in two. In only one of these patients did liver biopsy reveal cirrhosis.

Discussion

The presently reported experience with major surgical procedures in patients with a variety of myeloproliferative disorders is encouraging in regard to mortality and morbidity rates as compared to previous publications. Hemorrhage has been the most commonly reported complication, occurring in 75% of the complicated cases, and leading to 69% of the death.[15,21] Venous or arterial thrombosis and infection rank second and third on the complication list, both in patients with PV and MM.

The hemostatic abnormalities in these patients are complex, multifaceted, and not precisely defined. The increased viscosity associated with a high hematocrit is thought to lead to tissue hypoxia and consequent interference with vascular integrity. Quantitative platelet abnormalities in the form of thrombocytopenia may contribute to a compromise of hemostasis, while the less common thrombocytosis may be a factor in thrombosis, bleeding, or a combination of the two. A variety of qual-

TABLE 5. *Hemodynamic Findings in Patients With Suspected Portal Hypertension**

Measurement	Pressures (mm Hg) Normal	Case 1	Case 2	Case 3	Case 4
Rt. Atrium	0-5	4	2	5	4
Inferior Vena Cava	2-7	8	5	13	12
Free Hepatic Vein	4-10	10	9	14	15
Hepatic Venous Wedge	6-13	26	15	21	30
Cardiac Output (L/min)		4.97	5.83	8.28	5.92
Cardiac Index (L/min/m²)	2.7-5.0	3.23	4.10	3.97	3.92
Estimated Hepatic Blood Flows (ml/min/m²)	480 (±150)	1485	853	1100	1640
EHBF/C I	0.20	0.46	0.21	0.28	0.42
Varices		+	+	+	+
Ascites		–	+	–	+
Cirrhosis		–	–	+	–

*Some data previously published.[14]

itative platelet abnormalities has been reported.[2,14,21] These include: viscous metamorphosis, reduced dendrite formation and abnormal fragility, all contributing to a defective platelet fibrin network. Abnormal clot retraction, abnormal platelet aggregation and deficiency of platelet factor 3 have all been demonstrated and may further contribute to disorganization of the platelet fibrin network. In addition, the serotonin carrying capacity of platelets may be reduced, interfering with the hemostatic process of vasoconstriction.[21]

Abnormalities of plasma coagulation factors have also been defined in some cases of PV and MM. These include: a moderate reduction of fibrinogen, decrease in factor 5, 7 and prothrombin with a consequent prolongation of prothrombin time, and rarely fibrinolysis. The mortality and morbidity rates reported in this series are in keeping with those presented by Wasserman and Gilbert,[21] since all patients were prepared and none were markedly erythremic. It has been shown that reducing the hematocrit to less than 52% is associated with a reduction in the incidence of complications in PV and MM cases from 79% to 28%, and a reduction in mortality from 36% to 5%. An extended period of control, i.e., greater than 4 months, has been associated with a mortality rate that is ⅓ that present when the period of control ranged between 1 week to 4 months.[21] The need for meticulous surgery merits emphasis since technical and mechanical causes represent the most common factors in postoperative hemorrhage.

The therapy of MM and CML, including the hematologic manifestations, is generally based on transfusions, androgens, alkylating agents and ^{32}P. Although splenectomy may not alter the natural history of the disease, it is applicable as a palliative procedure to aleviate symptoms attributable to massive splenomegaly or multiple painful splenic infarcts, to reduce transfusion requirements or to correct significant thrombocytopenia and/or leukopenia. In 1937 Hickling[8] emphasized a high mortality following splenectomy in patients with MM. Jackson et al.[10] reinforced this concept and suggested that a major deterent was that splenectomy removed an important organ of blood formation. However, Green et al.[7] in 1953, presented a collective review in which they could demonstrate no support for this concept. As recently as 1966 a partial resection of the spleen for massive incapacitating splenomegaly in a patient with MM was carried out in an attempt to preserve an important site of extramedullary hematopoiesis.[13]

In reference to the palliative effective of splenectomy in patients with MM, Bouroncle and Doan[1] reported 14 of 24 patients had good results, while 5 could not be evaluated completely. Jensen[9] reported on 5 patients with MM who underwent splenectomy for hemolytic anemia, and in each instance there was a rise in hemoglobin and in 4 of the 5, the platelet count was elevated. None of the patients developed an exacerbation of the hematologic condition. Fishman and Ballinger[6] reported a similar experience with 5 patients in that a significant rise in platelets, neutrophiles and hemoglobin occurred in each instance. Recently, Silverstein and ReMine[18] reviewed their experience with 29 MM patients in whom splenectomy was performed for hemolytic anemia, thrombocytopenia, splenomegaly and portal hypertension. When compared with medical management for major hemolysis or radiation therapy for massive splenomegaly, their data suggested a better course for the splenectomy group. An increase in mortality and morbidity was noted in men, but the groups were not similar in that women tended to be younger when splenectomized and had a longer duration of illness before splenectomy. Our own experience and an extrapolation of the experience of others fail to reveal this suggested difference related to sex.

In order to distinguish cases where the role of the spleen is primarily that of an organ of red cell destruction from those cases where the spleen is a major organ of erythrocyte production, erythrokinetic studies using ^{51}Cr for red cell survival, ^{99}Fe for identifying the site of erythropoetic activity and ^{99m}Tc for measuring splenic red cell mass have been applied. Since it is now appreciated that the spleen is rarely, if ever a significant organ of extramedullary hematopoiesis in these patients and an adverse hematologic effect related to splenectomy has yet to be encountered, these studies are not carried out routinely in our institution preemptive to splenectomy in order to provide a basis for patient selection.

Increased portal pressure in patients with MM and massive splenomegaly may result from increased hepatic resistance due to cirrhosis or diffuse extramedullary hepatic foci. Another proposed cause of the increased portal pressure is increased portal flow, either unassociated with or superimposed upon increased hepatic resistance. Previous publications have reported that splenectomy alone in patients with MM has reduced portal pressure to normal levels,[4,9] and resulted in the disappearance of varices two months after splenectomy.[20] A number of cases have been reported in which splenic arteriovenous aneurysms unaccompanied by hepatic portal venous obstruction caused portal hypertension.[3] A case of variceal bleeding has been related to intrasplenic AV shunt, and after splenectomy, the varices disappeared.[19]

Evaluation, on theoretical gounds, of the increased portal venous flow necessary to increase portal pressure to levels greater than normal suggests that forward blood flow increases in physiologically possible ranges may result in hypertension in a low resistance portal venous system.[16] The presently reported intraoperative pressure determinations demonstrating reduction of portal pressure with splenectomy alone in patients with MM, coupled with the hemodynamic studies defining significant increases in estimated hepatic blood flow indicate that patients with MM, massive splenomegaly and portal hypertension should be thoroughly investigated in order to define that group for which splenectomy alone may correct the portal hypertension and its clinical manifestations.

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DISCUSSION

DR. WALTER F. BALLINGER, II (St. Louis): The subject of splenectomy from myeloproliferative disorders continues to have many controversial aspects. Dr. Schwartz has convincingly demonstrated in this presentation that splenectomy is indicated for palliation in some of these conditions such as myeloid metaplasia with myelofibrosis, but leaves the question unresolved for others.

His breakdown of indications for splenectomy is quite similar to ours. Furthermore, our morbidity and mortality data are almost identical to those presented by Dr. Schwartz today.

Opportunity for long term survival in our hands seems somewhat less optimistic and might perhaps reflect a difference in referral patterns in that patients may be seen earlier in the course of their disease by Dr. Schwartz and his group.

Two somewhat minor controversial points in reviewing the manuscript about the surgical management might be emphasized. The first, an old chestnut, is whether or not to drain the subphrenic space. Our attitude seems to be somewhat different from that expressed by Dr. Schwartz, not on the podium today, but in his manuscript.

We would rather not drain the space following splenectomy unless there is significant oozing from divided adhesions between the spleen and the diaphragm or unless there is a suspected or actual injury to the tip of the pancreas.

A second unsettled issue is related to the anticipation and management of post-splenectomy thrombocytosis. There is increasing evidence of thrombotic episodes, particularly in patients with myeloid metaplasia and chronic myelogenous leukemia, occurring not infrequently after splenectomy. The seriousness of this has been emphasized by the reports of mesenteric vein occlusions as reported by Boss this year and one such case included in the manuscript of Dr. Schwartz.

We think the use of acetylsalicylic acid as the antiplatelet agent has several appealing aspects.

The mechanism of its action has been thoroughly well worked out by Roth and Majares. It seems that very low doses of aspirin, as little as 300 mg will significantly alter platelet aggregation probably by inactivating an enzyme necessary for synthesis of prostoglandin E-2. As long as there are no bleeding tendencies or abnormalities of coagulation factors, aspirin should be taken in these doses.

Furthermore, by stopping aspirin, the effects can be completely reversed within one to two weeks with normal bone marrow producing normal platelets.

Clinical studies of prophylactic aspirin, although not conclusive, show a definite benefit in possible prevention of thrombosis, as described recently in England. Whether it will help the post-splenectomy thrombosis in these situations is unknown.

DR. PAUL C. KIERNAN (Washington, D.C.): President Hardy, a small group of patients substantiate Dr. Schwartz's thesis so beautifully presented. One of chronic myelogenous leukemia and two of myeloid metaplasia.

A 45-year-old man with myelogenous leukemia and evidence of hypersplenism with splenomegaly required daily multiple transfusions to maintain a hematocrit of 28.

An estimated 6000 gm spleen with huge vascular splenoperitoneal adhesions precluded splenectomy, at least in this person's hands, and suggested splenic artery ligation with resultant massive infarction and rapid decrease in the splenic size and marked improvement in all segments of the blood, a sharp drop in the need for transfusion and good palliation.

A 40-year-old man with extensive myelofibrosis of the marrow and pancytopenia required frequent blood transfusions because of the pancytopenia. An 1800 gm spleen was removed and since then normal blood counts have been maintained.

A 73-year-old male with pancytopenia required frequent transfusions. There was an absolute white count of less than 500 and platelets of 15,000-20,000. He survived an *alpha streptococcus* and *E. coli* sepsis and a 690 gm spleen was removed. The white count remains above 4000, hematocrit at 30 and platelets 40,000.

DR. CHARLES M. MCBRIDE (Houston): I was greatly interested in Dr. Schwartz's paper as working with Dr. Jeane Hester, one of our hematologists, we have been tackling this problem quite regularly recently.

We add one more indication to the ones Dr. Schwartz gave and that is the painful infarcts that are so common in the patient with chronic granulocytic leukemia. The resultant fever and the inability to eat adversely affect these patients.

Prior to starting our present protocol, I'm afraid we had a 35% mortality rate in operations on leukemic patients. We have now done 36 splenectomies, most of them in chronic granulocytic leukemic patients and 20% of these were in blast crisis at the time they were done.

We prefer the patients to have at least three courses of chemotherapy before we operate on them so that we know when their blood counts are going to bottom out. Then we prefer to operate on them just as the counts are beginning to recover. We prefer to have both normal white counts and platelet counts in these patients.

If we then have two of quad packs of platelets cross matched and we hope to have at least two HLA matches for these, we've found that we've had no significant problem. We do not drain and we do use the platelets immediately the spleen comes out and not before.

DR. RICHARD WILSON (Boston): President Hardy, I think Dr. Schwartz is certainly to be congratulated for his excellent experience with splenectomy in these unusual diseases. I would just like to add a word of caution to one group of myeloid metaplasia patients; that is those with severe thrombocytopenia.

We certainly agree with him about the ability to do a splenectomy safely for the other indications, but I think this group with platelet counts under 20,000 and falling, are the ones where the greatest risk exists. The rise in platelets after splenectomy in this group of patients is certainly less brisk, if even noticeable for quite some time, as compared to most other experiences with splenectomy.

We have found it necessary take extra and particular precautions to suture ligature all surfaces that are left behind that might bleed and to often use platelet transfusions.

The only two deaths that we have had in a very large series, somewhere around 25 patients with myeloid metaplasia, have been in two patients with severe thrombocytopenia that did not get any response at all and continued to bleed postoperatively.

I would like to know what has been the rate of platelet rise in his patients that were operated upon for thrombocytopenia?

DR. SEYMOUR I. SCHWARTZ (Closing discussion): In reference to Dr. Ballinger's jousting regarding the chestnut, I have no argument. I would agree with him in principle. We never drain the splenectomies for other immunologic diseases. But he alluded to the one indication for drainage, that is, a continuance of significant oozing that occurs quite frequently in these patients because of the highly vascular ligamentous attachments. For this reason, although we have attempted to be meticulous, we have more frequently than not drained these patients.

I think his suggestion regarding the use of aspirin for thrombocytosis is appropriate. We have not routinely used it and have had experience with one patient who went on to develop both mesenteric and renal vein thrombosis thirty days after surgery.

Dr. Kiernan brought up a very interesting point, that of ligation of the splenic artery if splenectomy is not feasible.

This is attractive in concept, but in fact rarely has been appropriate because in those circumstances in which we were confronted by a very large spleen and would have liked to take the other route, splenic artery ligation, we had to immobilize the spleen in order to get at the splenic artery and so we ended up with a classically executed splenectomy.

Dr. McBride brought out an indication to which I did not refer specifically but which is included under the category of symptomatic splenomegaly. You're certainly correct. Many of these patients complain of painful infarcts and this is one of the prime indications for splenectomy.

His reference to the group of leukemic patients is somewhat tangential. In our series, there are only four patients with chronic myelogenous leukemia, and the others could not be categorized as leukemia.

It does give me the opportunity to make an evangelical plea for the application of splenectomy early in the course of patients with leukemia of any type to alleviate a symptomatic splenomegaly and control of hypersplenism.

Dr. Wilson's point related to that of thrombocytopenia and particularly the severe thrombocytopenia. This has not been a major problem and in the four patients in whom splenectomy was carried out specifically for advanced thrombocytopenia, that is, platelet counts less than 25,000, they have done reasonably well. Three of them have improved. We do not manage any of these patients preoperatively with platelets because that's merely pouring the modality down the sink.

The spleen is removed and rapidly thereafter, 20 units of platelet packs are administered. It is true that these patients, unlike the ITP patients, have a slower rise in their platelet counts postoperatively.

Finally, although we have refuted the concept that operation and particularly splenectomy in patients with myeloid metaplasia can be carried out without a prohibitive risk, I would be most negligent if I didn't caution against a cavalier attitude.

Of all the patients in whom splenectomy is carried out for hematologic disease, those with myeloid metaplasia present the most distinct problems both intraoperatively with reference to the need for meticulous hemostasis and postoperatively too.

Treatment of Peptic Esophageal Stricture With Combined Fundic Patch-fundoplication

JOHN I. HOLLENBECK, M.D., EDWARD R. WOODWARD, M.D.

Forty-five patients treated for peptic esophageal stricture by combined fundic patch-fundoplication are reviewed. The operation afforded an acceptable result in 87% of the patients. There has been no operative mortality. The stricture represents transmural fibrosis of the distal esophagus. This fibrosis interferes with the physiologic function of the LES preventing receptive relaxation. This, however, does not affect the postoperative ability to swallow.

PEPTIC ESOPHAGITIS with esophageal stricture represents two distinct entities that must be corrected if a long-term, satisfactory result is to be obtained. The strictured esophageal lumen must be enlarged and the associated gastroesophageal reflux prevented. We have combined the fundic patch of Thal[9] for correction of the stricture and the Nissen fundoplication[5] to prevent reflux. Initially, we used only the Thal patch, but soon found that the patch is susceptible to gastroesophageal reflux and recurrent stricture. This report summarizes our results of the combined Thal-Nissen operation through 1974. In this review we shall also discuss the effect of transmural esophageal fibrosis within the distal esophagus and the physiologic function of the high pressure zone created by the fundoplication.

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Material

Thirty-four males and 12 females comprise the patient population. They range in age from 3 to 85 years. All patients in this group had firm, fibrous strictures which were difficult or impossible to safely dilate. All strictures were a result of gastroesophageal reflux. Three patients in this group have scleroderma and resultant reflux with stricture formation. Details of two of these patients are presented elsewhere.[6]

Preoperative studies included barium contrast examination and esophagoscopy with biopsy. Esophageal motility and pH reflux studies were not generally done because of the difficulty encountered in passing the catheters into the stomach. Postoperative data for this report were obtained by outpatient clinic visits, inpatient admissions, and telephone or letter contact wtih patients or their referring physicians. The technique of this procedure is described in an earlier publication.[10]

Results

Of the 46 patients in the study group, one patient was lost to followup. Twenty-six patients were followed longer than 3 years, 5 greater than 2 years, 9 greater than

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TABLE 1. *Results–45 Patients*

Good	31	(69.0%)	87%
Fair	8	(18%)	
Poor	6	(13%)	

one year, and 5 less than one year. We classify our results as *good* if the patient: 1) can eat any food with minimal or no dysphagia, 2) required no dilatations after the early postoperative period, and 3) has no symptoms of gastroesophageal reflux. Patients who: 1) require occasional dilatation (no more frequently than every three months) or 2) have dysphagia for some foods or 3) have mild reflux symptoms are considered as fair results. Significant dysphagia, need for frequent dilatations or recurrent reflux esophagitis are indicative of a poor result.

Thirty-one patients (69%) are classified as good results. Eight of the 45 or 18% are considered fair results and six or 13% have poor results. Thus, 87% of the patients in the study group have acceptable results from their operation (Table 1). The apparent reasons for the poor results are summarized in Table 2.

There was no operative mortality in this series. Complications of operation are summarized in Table 3. Postoperative pneumonia occurred in 5 patients and atelectasis occurred in two. One patient was felt to have had a pulmonary embolus. Four patients developed wound infection and one a wound dehiscence. Esophageal leak occurred twice and both times was treated successfully by total parenteral alimentation and chest tube drainage. There were two episodes of cardiac arrhythmias that responded to medication, one patient with prolonged ileus, and one case of acute gastric dilatation.

Postoperative esophageal motility studies were obtained in 11 patients. All motility tracings showed normal peristalsis within the body of the esophagus. There was an adequate high pressure zone (HPZ) measuring from 8 to 12 cm of water in all 11 patients studied. However, the created HPZ does not function like the normal lower esophageal sphincter (LES). Deglutition resulted in receptive relaxation within the HPZ in only one of the 11 patients. This contrasts with patients who have had only a Nissen fundoplication. Receptive relaxation is seen in the HPZ of these patients who had no pre-existing stricture.

TABLE 2. *Apparent Reason for Poor Results*

Thal only followed at a later date by Nissen fundoplication	2
Incomplete Nissen fundoplication	2
Malignant stricture	1
Periesophageal scar causing mechanical esophageal obstruction	1

TABLE 3. *Complications*

Mortality	0
Morbidity:	
Pulmonary infection	7
Pulmonary embolus	1
Wound infection	4
Wound dehiscence	1
Esophageal leak	2
Other	4

Discussion

The combined Thal-Nissen operation is reserved for patients with firm, fibrous, transmural strictures which cannot be easily or safely dilated. Other reports[2,3] state that reflux-induced esophageal strictures can be treated by dilatation or finger fracture combined with an anti-reflux procedure. We do not agree that this is the case with the transmural stricture because it represents a scar contracture within the wall of the esophagus (Figs. 1 and 2). As with all scars, there is a three dimensional contraction. Esophageal scar decreases the lumen by circumferential contracture and the length is reduced by longitudinal contracture. The loss of length results in an "acquired short esophagus" and this makes the maintenance of the intra-abdominal gastropexy most unsure. Fracture of the stricture disrupts tissue integrity resulting in the formation of granulation tissue which is followed by fibroblast proliferation, collagen deposition and recurrence of the scar. Addition of an anti-reflux procedure following fracture of the stricture will not prevent this biological phenomenon of scar formation. Because peptic esophageal stricture represents a scar contracture, we feel that the fundic patch introduced by Thal represents the operation of choice for esophageal stricture. The patch provides tissue with an excellent blood supply which is easily transferrable to the stricture site. This allows replacement of the tissue loss by scar contraction with pliable, well-vascularized tissue. We have earlier reported[11] that the Thal patch is subject to injury from esophageal reflux if unaccompanied by an anti-reflux procedure. Four of 5 patients who had the Thal patch alone developed recurrent stricture from persistent gastroesophageal reflux. We, therefore, feel the anti-reflux component is mandatory and the Nissen fundoplication has proven its effectiveness. In those patients who have undergone previous gastric surgery or have a long stricture, there may not be enough fundus to perform a complete wrap. This has been the case in approximately 15% of the procedures in our series. We have employed either partial Nissen wrap or the Belsey[7] type anti-reflux procedure in these patients. Although the number of cases is small, we seem to be obtaining better results with the Belsey maneuver than the partial Nissen wrap.

The complete Nissen wrap does restore a distal high

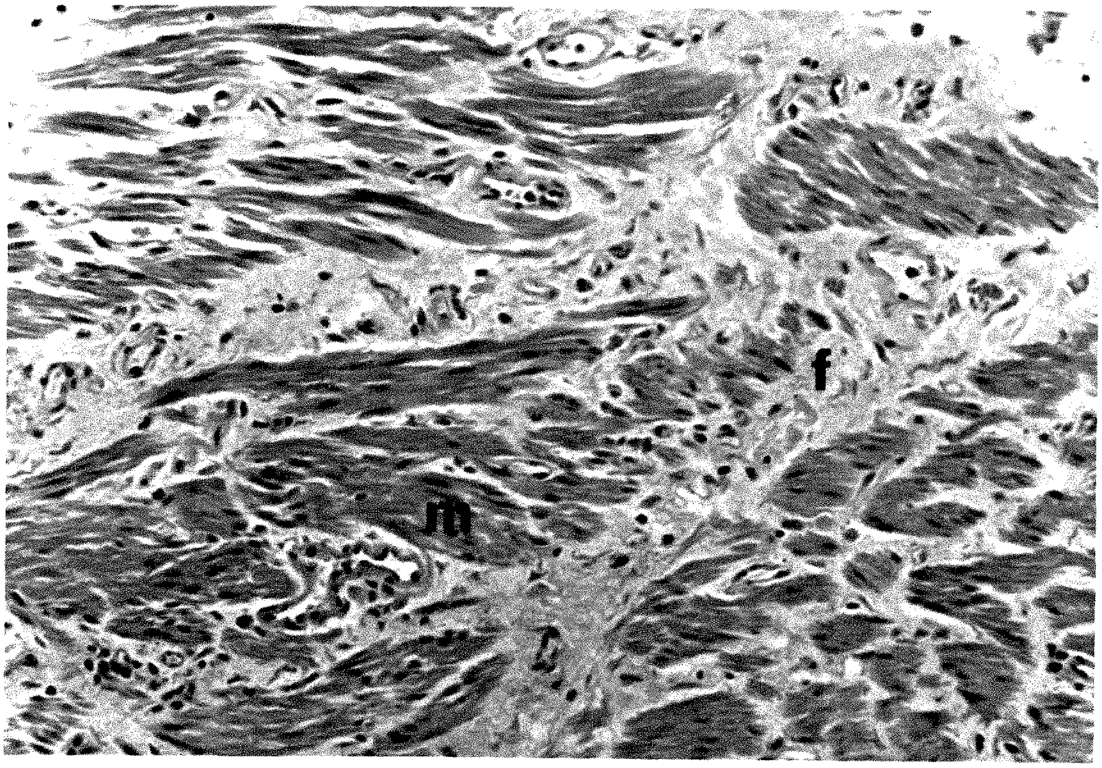

FIG. 1. Biopsy of an esophageal stricture demonstrating fibrous tissue (f) within the musculature (m) (H + E original magnification × 100).

pressure zone within the esophagus. The mechanism by which this occurs is currently being debated. Lipshutz, et al.[4] have shown that the Hill posterior gastropexy and the Belsey Mark IV repair restore resting lower esophageal sphincter tone along with a normal response to mechanical and neurohumoral stimulation. Intravenous pentagastrin administration produces contraction of the LES in these patients. They suggest return of normal resting tone

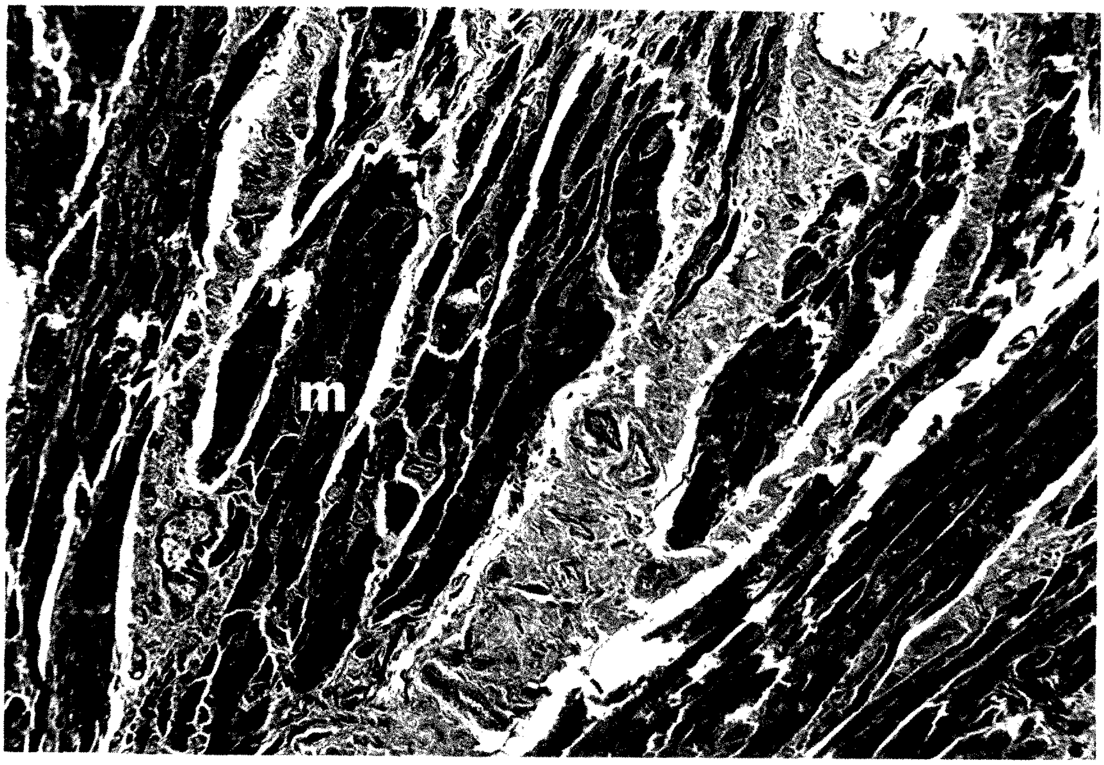

FIG. 2. Biopsy in the region of the lower esophageal sphincter demonstrating infiltration of muscle (m) by fibrous tissue (f) in a patient with reflux-induced esophageal stricture (Masson trichrome original magnification ×40).

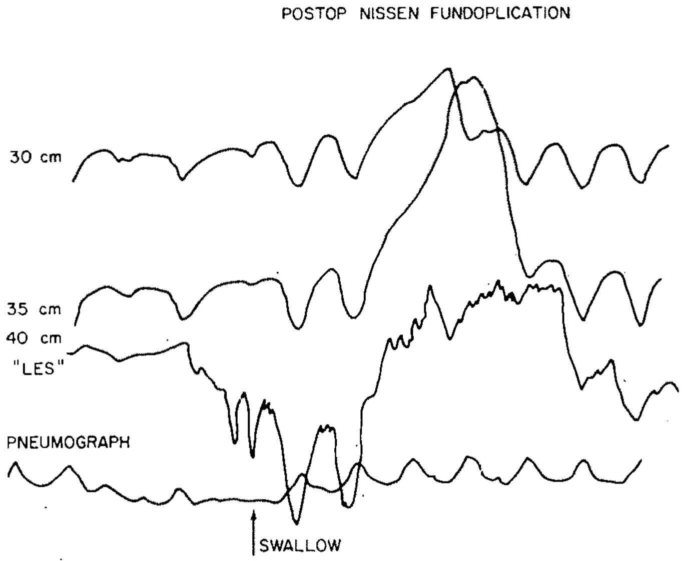

FIG. 3. Esophageal motility tracing of a patient following Nissen fundoplication demonstrating receptive relaxation of the lower esophageal sphincter during deglutition.

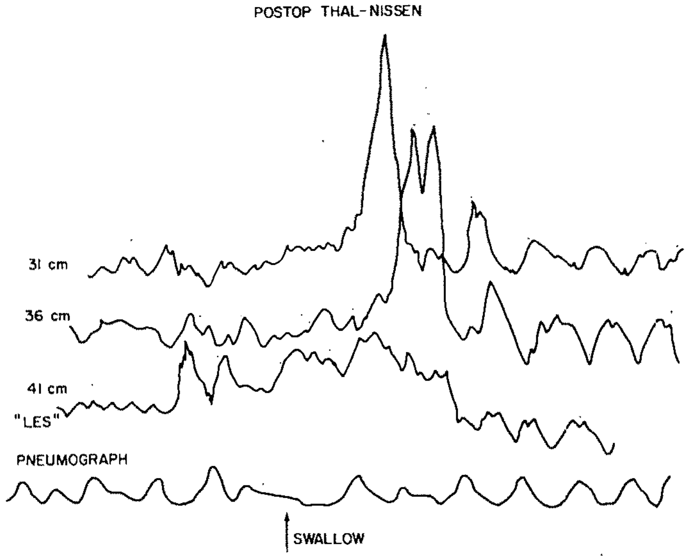

FIG. 4. Esophageal motility tracing of a patient following the Thal-Nissen procedure showing there is no receptive relaxation of the lower esophageal sphincter with deglutition.

optimizes the length-tension characteristics of the lower esophageal sphincter muscle allowing it to function physiologically. Others,[1,8] have disagreed with their conclusions. We have found that the Nissen fundoplication restores resting lower esophageal sphincter pressure while the physiologic characteristic of receptive relaxation of the LES remains intact (Fig. 3). However, 10 of 11 patients following a Thal-Nissen repair of esophageal strictures do not demonstrate this (Fig. 4). This may be attributed to the longitudinal incision made in the esophagus at the LES while doing the Thal portion of the repair. However, we believe that the LES does not have normal characteristics in these patients due to the transmural involvement of the LES by fibrosis. The fibrous tissue prevents the LES from responding properly to physiologic stimuli.

The incidence of carcinoma is low in peptic stricture of the esophagus, but it does occur. We have one such patient in our series. This patient had a 35-year history of symptomatic reflux esophagitis. Endoscopic biopsies were interpreted as showing only acute and chronic esophagitis. However, a small portion of the stricture sent for permanent section at operation showed carcinoma. Because of this experience we strongly recommend intraoperative biopsy of the stricture and frozen section pathologic examination.

It is interesting to note that 8 of the 46 patients (17%) in this series developed symptoms of dysphagia subsequent to nasogastric intubation for other procedures. In all 8, symptoms of dysphagia developed within 2 weeks to 4 months following nasogastric intubation even though the intubation lasted as short as 12 hours. This points out a need for a careful history of gastroesophageal reflux in any patient who will require an indwelling nasogastric tube. If postoperative gastric decompression is planned in a patient with gastroesophageal reflux symptoms, a temporary gastrostomy should be considered.

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DISCUSSION

DR. DAVID B. SKINNER (Chicago): I have followed this experience of Dr. Woodward and his colleagues over the past five years with great interest and believe they have clearly demonstrated several important facts for us.

First, the fundic patch operation by itself clearly does not prevent esophageal reflux, subsequent esophagitis, stricture and bleeding. Similarly to Dr. Woodward's experience, my former colleagues at Johns Hopkins and I have previously reported five out of six patients treated by the standard Thal operation developed severe complications with persisting reflux. The operation was judged a failure in that group.

Another point has been made today that is essential, I believe, both from Dr. Woodward's experience, ours and others. The addition of a full 360° fundal plication wrap around the intrathoracic esophagus will serve as an effective mechanical barrier to reflux.

(Slide) This is from a previously reported primate study where we did a Thal operation in the chest and postoperatively there was no high pressure zone. We then reoperated and did the full wrap and there was an effective barrier. These animals had free reflux before the first operation but not after reoperation.

Another point raised by Dr. Hollenbeck is what is the nature of this high pressure zone? We believe that in normal people, it is the intraluminal expression of both an intramural and an extrinsic pressure applied on the esophagus, but it is not an exclusive property of the distal esophagus and can be recreated mechanically as was shown today and by other studies.

We do find a high pressure zone restored by a variety of other operations, which raises some question about whether this is really a property of the esophagus.

For example, here is a high pressure zone postoperatively which seems to relax with a swallow. This is in a gastric tube, after a collis gastroplasty operation and Mark IV repair. The high pressure zone is located in this section of the gastric tube rather than up in the distal esophagus.

Similarly in our colon interposition series we find that a high pressure zone can be located in the colon segment as it passes through the diaphragm. This pull-back tracing shows a reasonable high pressure zone which does rise in response to abdominal compression just as the normal distal esophagus will do.

So we believe at this time, the most useful concept is to consider the high pressure zone to be a barrier to reflux from whatever cause, extrinsic or intrinsic, rather than to represent an intrinsic distal esophageal sphincter.

Finally, we disagree with the authors' approach of using one operation for all reflux strictures. The degree of pathology is really quite variable as is often the type of prior surgery when we see these patients.

This last slide summarizes our experience with a series of patients, who have been treated by a range of operations tailored to the extent of pathology and operative findings.

Some of the operations are obviously much more simple than the Thal operation. Whereas, other patients, particularly those who have had multiple previous operations require a more extensive procedure of resection and bowel interposition.

This last operation has given us our best results including in one patient with a previous Thal procedure from Northern Florida. We suggest that therapy should be tailored to the degree of abnormality as determined before and during surgery. If you do do the Thal procedure, you must do the full fundoplication.

DR. JOHN L. SAWYERS (Nashville, Tennessee): Drs. Hollenbeck and Woodward have presented excellent results for a difficult operative problem. Unfortunately, patients with reflux esophagitis are too often managed by non-operative methods until an esophageal stricture results which makes surgical correction difficult.

I have had the privilege of reviewing their manuscript and wish to congratulate them on the significant contribution that they have made with their esophageal motility studies.

We are in complete agreement with the authors that the basis for surgical repair of these patients is utilization of an effective anti-reflux procedure, and the Nissen fundoplication has proven effective. However, we would disagree about the necessity for the Thal fundic patch.

I wouldn't disagree with Dr. Woodward without support from others and so I have some international support. Hayward from Australia, Naef from Switzerland and Hill from the United States have demonstrated that forceful dilation of the esophageal stricture combined with an effective anti-reflux operation is effective therapy.

These strictures do not recur if esophageal reflux into the esophagus is prevented. Followup studies on such patients extend now to over eight years.

Lynwood Herrington and I recently reviewed our experience with patients who had undergone operation for reflux esophageal stricture.

(Slide) A two team approach of forceful dilation of a stricture under anesthesia using peroral dilation through an esophagoscope combined with retrograde dilation through a gastrostomy incision is used to dilate those patients who have a very firm fibrous stricture. Following forceful dilation, a Nissen fundoplication is done to prevent future reflux. The type of stricture that we're speaking about is illustrated on the following slide.

(Slide) There's a very tight stricture here and after forceful dilation with the Nissen fundoplication, you can see the deformity from the fundoplication but no residual stricture.

(Slide) Again a tight stricture, and you can see the barium marshmallow retained above the stricture. Here's a picture of the postoperative result with no residual narrowing.

Sixty-nine per cent of our patients have had an excellent result, 25% a good result and 6% a result that was less than desirable but still improved over the preoperative status. There has been no operative mortality.

Our results and those of Hill and others indicate that patients with peptic esophageal stricture can be safely and effectively treated by dilation alone without opening the esophagus when combined with an effective anti-reflux procedure.

DR. HIRAM POLK, JR. (Louisville, Kentucky): I am uncomfortable in the sense that I rise to express disenchantment with a procedure that is obviously of such proven and impressive excellence. I would like to describe our experience with this particular operative procedure in four patients. I will not give you the specific details, but only remind you that in four patients we achieved 18 complications. Please note that it required Dr. Woodward 46 patients to achieve 19 complications.

The four patients have had some 15 operations in a total of 282 hospital days and unfortunately when last seen all of them could not swallow or were dead. However, the real point of the presentation is to suggest that there must be a problem in patient selection. I would in all seriousness like to ask Dr. Woodward and Dr. Hollenbeck to discuss their selection. Obviously, we choose very poorly!

We do want to confirm the observation Dr. Skinner has made, however. The operation of intestinal interposition was dropped in many centers a few years ago for alleged high risk.

Having had some experience with intestinal segments with Dr. Bricker, we've done a series of 16 patients who had the old Merendino operation. The impressive thing about this is, of course, that all 16 of the patients have done well. They continue to do well over a mean followup now of four years and only two of the 16 patients have required reoperation. Both of those were for relief of intestinal obstruction; all of them swallow well.

The key point here is, of course, to appreciate that Drs. Woodward, Sawyers and others are trying to define the treatment of a very difficult illness.

I do wish in closing they would respond to something about which operation for which stage of the disease (i.e. what degree of esophagitis)?

DR. DAVID P. BOYD (Boston): This is an impressive piece of work and it's persuasive. In the first place, it's a large experience with a relatively rare complication of a common condition; then it's a good clinical record. No patients were lost and there were only five redos in 49 cases.

I don't think we can top this. As has been said it makes one realize that this manifestation of foregut ulcerative disease is being treated too conservatively for too long.

With apologies to Dr. Skinner, I think one value of this paper is that it takes the spotlight away from visceral interposition which has had center stage for a long time. The essential problems are clearly stated.

We must restore the esophageal lumen and we must keep it open by an anti-reflux procedure.

Dr. Hollenbeck prefers Nissen's operation as does my associate, Dr. Ellis.

When the stomach will not go where it properly belongs, I have used fundal plication without a pang. It seems to work, as Dr. Skinner and the essayist show.

My own strong preference is for the less unnatural posterior plication of Hill.

Much less settled is how to get the esophagus open and here I part with the authors. Is there really an undilatable stricture? I am prepared to doubt it formally. So respected a protagonist of intestinal interposition as Belsy has called dilatation of the esophagus the most dangerous operation in thoracic surgery. If so, I have no case, but I doubt this even more.

I think parenthetically we may be spawning a generation of flexible endoscopists who are strangers to the swallowed silk thread, the filiform bougie, and the Godsend which is known as the Maloney dilator. Perhaps we should get this sophisticated esophageal work back where it belongs.

If a given stricture is too worrisome, Sir James Walton's retrograde and to-and-fro dilatation through a feeding gastrostomy is still available although it has long been forgotten.

For the ordinary case which won't dilate readily, dilatation can still be accomplished perorally with the mobilized esophagus in the surgeon's hand. It's amazingly simple and effective.

I think we should keep out of the diseased unfriendly esophagus if possible.

Whatever means we use, we must restore the lumen as has been shown with such force and clarity this afternoon. If we do this and then we do an operation to stop ulcerogenic acid pepsin reflux, the esophagus will heal and will stay healed.

DR. EDWARD E. MASON (Iowa City, Iowa): Dr. Shirazi has recently reviewed and reported our experience with this disease in 26 patients over the last nine years. We have also felt that you had to have a good anti-reflux procedure, but we have gone in the direction, as indicated by the last speaker, of dilatation, usually preoperatively, if this is not possible intraoperatively.

Dr. Shirazi has added a little intraoperative test to make sure that the fundoplication does prevent reflux. The duodenum is occluded with the surgeon's fingers. The stomach is filled with saline. The tube is pulled back into the esophagus and compression of the stomach is used while the anesthetist watches for saline draining from the esophageal catheter.

(Slide) The patients dilate themselves beginning about ten days after the operation and daily for three months; then twice a week for another three months. Of course, this may be considered a disadvantage, I suppose, although they don't seem to mind it too much.

DR. J. I. HOLLENBECK (Closing discussion): We would agree with Dr. Skinner that the high pressure zone seen is probably mechanical as it appears in his work.

The patient selection, I think, is really the next point that needs to be made. This hopefully will answer the questions raised by both Dr. Boyd and Dr. Mason. Basically, we attempt to employ oral dilatation with the Hurst mercury weighted bougies in all stricture patients. If we are unable to do this with relative ease, and I think that's the real question—what is relative ease?—we use the Thal-Nissen procedure. Generally we do not use retrograde dilatation or intraoperative maneuvers to dilate the stricture.

Dr. Sawyer, previous experience from 1953 to 1964 in 39 patients using finger fracture, vagotomy, and pyloroplasty with hiatus hernia repair did not produce satisfactory results. This experience is what turned us against that particular method of therapy. We do have a number of patients with esophageal stricture whom we have treated with dilatation and anti-reflux procedure and obtained a quite satisfactory result. We feel that these strictures were not transmural, thus can be treated in this method.

As to when we do use the interposition procedures, which was Dr. Polk's question, we reserve the interposition for failures from the Thal-Nissen procedure. We do agree that the interposition is an excellent operation. The only thing that we have against it is the reported high mortality and morbidity. We feel the fundic patch-fundoplication method offers an operation with less mortality and morbidity.

We feel strongly that transmural scar is not changed by the addition of an anti-reflux procedure; that is to say the pathology of transmural scar will persist even though gastroesophageal reflux is prevented.

Lesions of the Segmental and Lobar Hepatic Ducts

WILLIAM P. LONGMIRE, JR., M.D., RONALD K. TOMPKINS, M.D.

Despite reports to the contrary, unobstructed drainage of 50% of an otherwise normal liver through either the right or left uninfected hepatic duct is adequate to restore normal liver function, even if the obstructed lobe remains in place. An undrained liver lobe, if present, may require no further treatment. As long as it is completely obstructed and uninfected, it will undergo a progressive asymptomatic atrophy. Cholangitis invariably develops behind a partial lobar ductal obstruction, producing jaundice, pruritis, and fever. Unless unobstructed, uninfected biliary flow can be achieved through a segmental or lobar duct, it is better that the duct be completely obstructed and the affected liver parenchyma allowed to atrophy, provided there is normal biliary flow from the residual 50% of liver. This concept is important in the management of injured anomalous segmental or lobar hepatic duct and in the palliative treatment of bile duct carcinoma. Localized intrahepatic infections communicating with abnormal biliary ducts will require hepatic resection of the infected parenchyma and ducts for cure. The abnormality may be saccular dilatation of the intrahepatic ductal system with abscess formation or intrahepatic abscess associated with stenosis of the ductal system from trauma to the duct, to the duct and liver, or to retained intrahepatic stones. Diffusely situated intrahepatic abscesses secondary to ductal abnormalities can be treated with systemic antibiotics, local drainage of a dominant abscess, and efforts to improve biliary drainage.

IT HAS BEEN DEMONSTRATED in man that, after major resection of the liver, adequate hepatic function can be maintained by as small a residual segment of liver tissue as approximately one-fourth of the organ's normal volume.[16,19,27] The effects of obstruction of a segmental or lobar duct that drains an otherwise intact functioning human liver unit (segment or lobe), however, are not precisely known, and the limited pertinent reports in the literature are confusing and, at times, apparently contradictory.

Localized biliary obstruction, however, is but one of the effects of a variety of clinical conditions that may involve either the intra- or the extrahepatic lobar or segmental hepatic ducts, producing obstruction, biliary infection, or external biliary fistula, either singly or in combination. The hepatic and systemic effects of these lesions and their management are the focus of this report.

From the Department of Surgery, UCLA School of Medicine, Los Angeles, California 90024

Anatomy

The functioning unit of the intrahepatic biliary system was first clearly presented by Hjortsjo,[13] who, in 1948, reported, on the basis of observations on corrosion casts, that the hepatic arteries, bile ducts, and branches of the portal vein had a segmental distribution within the liver. The studies of Healey and Schroy,[12] in 1953, also supported this concept and demonstrated that every major artery of the liver supplies a definite segment of hepatic parenchyma and that every bile duct drains a definite segmental area of the liver. Within the normal liver, other than the regular confluence of smaller ducts into larger ones, there is no anastomosis of bile ducts or collateral bile exit pathways to develop in the face of obstruction.

McArthur et al.[21] studied in detail the extraparenchymal hilar hepatic ducts proximal to their confluence to form the common hepatic duct, noting that a 3 cm section of left hepatic duct regularly is present outside of the liver parenchyma from the site where the duct is formed by the confluence of its two major branches until it joins the right hepatic duct. The extraparenchymal right hepatic duct was usually less than 1 cm in length.

The biliary system below the hepatic duct confluence, the portion of the ducts most often exposed to manipulation during the performance of cholecystectomy, the

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second most common intra-abdominal surgical procedure in America, abounds with anatomical variations. As Cole[5] commented a number of years ago: "In no region of the body are anomalies so common as in the bile ducts and adjacent blood vessels. It is, therefore, impossible to present any pattern as the 'normal'; a composite of specimens least abnormal becomes the substitute for normal anatomy in this area." In a series of 200 dissections of the extrahepatic bile ducts, Flint[7] found only 69 to conform with the arrangement of vessels and ducts as given in textbooks of anatomy. The most common anomaly involving the hepatic ducts was that of aberrant or accessory right hepatic ducts encountered in 29 examples. In 9 cases, the aberrant hepatic duct ran from the right lobe into the right hepatic duct or into the proximal portion of the common hepatic duct where it was high enough in the hilus of the liver that injury during cholecystectomy was unlikely. The aberrant right hepatic duct entered the lower portion of the common hepatic duct or the junction of the cystic and common duct in 19 cases at a point where it might readily be injured during cholecystectomy unless the area were dissected meticulously. In one case the aberrant duct entered the cystic duct (Fig. 1).

Flint stated that the size of these aberrant ducts varied: "The smallest is only large enough to admit a good sized bristle. The largest is as big as the right hepatic duct. The most common is half way between these limits, that is to say, it is quite a considerable duct." Such aberrant hepatic ducts have generally been reported to occur in 10% to 18% of cases[1,23,24] and to have a diameter that approximates that of the cystic duct.[1]

A second anomaly of the hepatic ductal system of major concern to the surgeon is a low confluence of the left and right hepatic ducts, either with or without the cystic duct entering the right hepatic duct (Fig. 2). This arrangement was found in one-fourth of the major duct anomalies identified by Daseler et al.[6]

The unrecognized division of a small duct passing directly from the liver into the gallbladder has been listed for many years as one of the principal indications for the use of drains after cholecystectomy. Despite recent studies that have questioned the existence of such congenital cholecystohepatic ducts, small open ducts have been well documented in the bed of the gallbladder, passing directly into the liver parenchyma after cholecystectomy.[14,26,29,34] Goor and Ebert[10] reported the division during cholecystectomy with reanastomosis of an aberrant hepatic duct that ran from the right lobe into the common hepatic duct within the wall of the gallbladder. Thus, it seems that small segmental ducts do, on rare occasions, course from the liver parenchyma in intimate contact with the wall of the gallbladder into either the gallbladder itself or into the ductal system and that these ducts may be severed during cholecystectomy (Fig. 3). It has been repeatedly expressed that free bile does not appear in the bed of the gallbladder to alert the surgeon that such a duct has been divided.

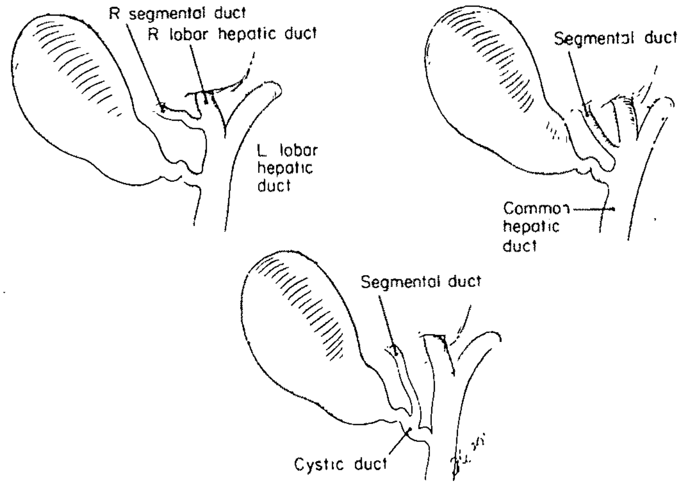


FIG. 1. Common anomalies of extrahepatic segmental and lobar ducts of surgical importance.

Experimental Pathophysiology

Braasch et al.[3] interrupted from one to 5 of the 7 segmental hepatic ducts of the dog and performed a variety of hepatic tests. They found that the extent of deviation from normal was related to the fraction of the total bile outflow obstructed. Serum bilirubin was least affected. Of 21 animals studied, in only four did the serum bilirubin concentration rise above 1 mg/100 ml, and it was necessary to interrupt 3, 4, or 5 ducts in these animals. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase concentrations showed the greatest abnormalities. These tests returned to normal in 2 to 3 months' time in most of the animals. Other abnormal hepatic tests gradually returned to normal as the

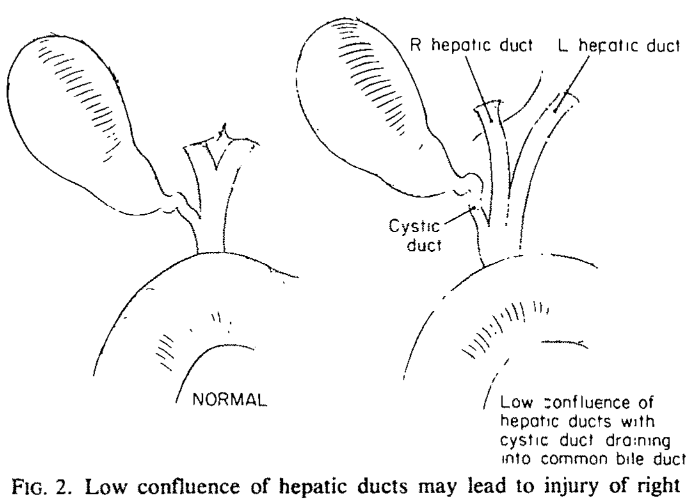

R hepatic duct
L hepatic duct
Cystic duct
NORMAL
Low confluence of hepatic ducts with cystic duct draining into common bile duct

FIG. 2. Low confluence of hepatic ducts may lead to injury of right hepatic duct during cholecystectomy.

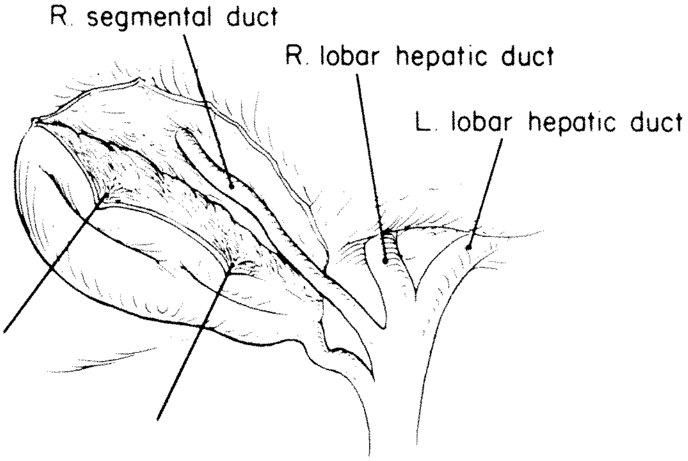


FIG. 3. Anomalous segmental duct in bed of gallbladder that may be injured during cholecystectomy.

obstructed liver parenchyma atrophied and the unobstructed liver underwent hyperplasia. Unobstructed lobes were found to double their weight after obstruction of approximately 40% to 60% of the biliary drainage system. In earlier studies,[11,22] which may have lacked sensitive laboratory test techniques, ligation of up to 80% of the biliary outflow system was found to result in increased urinary bile excretion but without a concomitant increase in serum bilirubin.

Clinical Reports

Clinically, pruritis, the most distressing symptom of chronic uninfected biliary obstruction, is generally related to the degree of hyperbilirubinemia, but the extent of ductal obstruction necessary to produce a clinically significant hyperbilirubinemia in man has not been clearly defined. Likewise, factors other than obstruction have not been fully evaluated, either from the standpoint of their relationship to the degree of hyperbilirubinemia or with respect to their role in the production of pruritis and associated disabling clinical symptoms, including the eventual serious deterioration of hepatic function. Pruritis is generally thought to be caused by the irritation of cutaneous sensory nerves by retained bile salts, and its intensity has been related to the concentration of bile salts in the system. Sherlock[30] questioned this assumption and pointed out that current information merely indicates that itching is caused by some substance normally eliminated in the bile. That itching disappears when liver cells fail suggests that the substance is manufactured by the liver.

Stafford and Issacs[32] reported upon two elderly patients (70 and 75 years of age) with calculous obstruction of the left hepatic duct accompanied by mild jaundice, congestive heart failure, and, in the second case, cholangitis: (Case 1, serum bilirubin, 2.3 mg/100 ml, alkaline phosphatase, 18 units; Case 2, serum bilirubin, 2.3 mg/100 ml, alkaline phosphatase, 24.6 units). It was their conclusion that jaundice occurred because the functional reserve of the liver suffered a double impairment from blockage of the left hepatic duct and congestive heart failure. It is noteworthy that the jaundice in one patient cleared after digitalization, bed rest, and probable subsidence of the cholangitis before operative relief of the duct obstruction.

Cattell and Braasch,[4] in their report of difficult repairs of benign strictures of one or both hepatic ducts, commented that the symptomatology in patients in whom only one hepatic duct is obstructed is different from the classical picture of common duct obstruction in that the jaundice is less intense, pruritis is a prominent feature, and the urine is dark but the feces remain normal in color. They included in their series 11 instances in which the left hepatic duct alone could be located and anastomosed, either to the lower end of the duct or to the jejunum. Recognizing the uncertainties of such difficult reconstructions, it is important to note that, at the time of their report, three patients with only a functioning left hepatic duct were alive with satisfactory results more than 3 years following operation.

Braasch and Preble[2] later reported in abstract on 4 of their cases and an additional 3 cases from the literature of a specific syndrome associated with the obstruction of a single hepatic duct, without significant decompression by internal or external fistula and characterized by jaundice, dark urine, stools containing bile pigment, and unilateral enlargement of the obstructed lobe of the liver. They postulated that the obstructed lobe produces an altered bilirubin "which the unobstructed lobe secretes with notable inefficiency." They suggested that hepatic lobectomy might be useful in the treatment of unilateral obstruction from benign stricture. One year later, Mistilis and Schiff[25] reported such a jaundiced patient with malignant unilateral left hepatic duct obstruction in which the jaundice was only temporarily reduced by drainage of the right hepatic duct but relieved after removal of the obstructed left lobe. They commented: "Experience in this case confirms previous reports of the occurrence of jaundice in patients with unilateral hepatic duct obstruction. While regurgitation of bile from the obstructed lobe is the factor apparently responsible for the development of jaundice, the persistence of icterus in spite of adequate bile drainage from the unobstructed lobe and its disappearance following surgical removal of the affected lobe raises the question of whether the human liver is able to excrete conjugated bilirubin delivered to it."

Based on the observation of 4 patients with strictures of bile ducts of a segment or lobe, Braasch et al.[3] concluded that humans respond in a manner comparable to that observed in dogs, that is, elevation of serum bilirubin

TABLE 1. *Segmental or Hepatic Bile Duct Injury Without Infection*

Patient	Cause	Duct Injured	Treatment	Result	Remarks
E.K.	Cholecystectomy	Common hepatic	L. hepatico-jejunostomy	Well	R. hepatic duct not reconstructed
W.E.	Cholecystectomy	R. dorsal caudal	Ligated?	Well	Dorsal-caudal segment not seen on cholangiogram
		Ventral-cranial segmental	End-to-end anastomosis		
A.A.	Cholecystectomy	Common hepatic.	Hepatico-jejunostomy		External biliary fistula closed spontaneously
		Dorsal-caudal segmental	Ligation	Well	

with major portions of the bile outflow obstructed, atrophy of obstructed lobes, and hypertrophy of unobstructed lobes. The inference is made that obstruction of a large segmental duct draining one-third of the liver substance or of either the right or left hepatic duct is sufficient to cause a significant elevation of the serum bilirubin. Their cases, however, were all quite complicated, and the long histories of repeated operations, infection and cholangitis, partial degrees of obstruction, and varying degrees of generalized depression of hepatocellular function make difficult evaluation of the sole effects of segmental or lobar duct obstruction.

George[8] reviewed the treatment of carcinoma of the bile ducts at the confluence of the right and left hepatic ducts and commented that "it is essential to relieve the obstruction to the right lobe of the liver, as relief of the left lobe only will not cause effective disappearance of jaundice." Such a statement, however, does not reflect the true anatomical equality of the parenchymal liver mass of the right and left lobes. Our experience demonstrates that drainage of the left hepatic duct alone will relieve jaundice (c.f. Case H.C., Section on Hepatic Duct Carcinoma).

From these somewhat conflicting reports of others, together with our own experience with isolated segmental or lobar hepatic duct obstruction, it is apparent that four factors are of paramount importance in the determination of the clinical course of a patient with such a condition: 1) degree of obstruction, i.e., complete, partial, slight; 2) extent or percentage of hepatic parenchyma with obstructed drainage; 3) presence or absence of infection in the ductal system; 4) condition of the unobstructed liver.

Fortunately, the surgeon is infrequently concerned with problems related to lobar hepatic ducts, but it is important to be acquainted with lesions that involve these structures and to have some knowledge of the basic principles to be used in their treatment.

Classification of Lesions

Based on a review of more than 50 patients seen at the UCLA Hospital, segmental and lobar hepatic duct lesions have been classified into the following groups: 1) Segmental or hepatic bile duct injury without infection; 2) Segmental or hepatic bile duct injury with infection; 3) Congenital hepatic duct lesions; 4) Intrahepatic stones; 5) Hepatic duct carcinoma.

Segmental or Hepatic Bile Duct Injury Without Infection

If, during the course of cholecystectomy, a segmental duct or the right hepatic duct is injured, what can be the patient's anticipated course? Kune[15] cautions that "if the surgeon encounters more than two ducts issuing from the liver, on no account should he divide or ligate any of them, assuming it to be an accessory duct, because serious consequences will follow." Longo and Masumana[20] found aberrant hepatic ducts in 10% of their cases studied with cholangiograms. They concluded that aberrant bile ducts occur more frequently than is generally believed, that little harm may result should a small aberrant duct be injured during cholecystectomy, but that if a larger duct is injured and not detected and repaired, bile peritonitis will result.

Smith[31] recommends that small or filament-like accessory ducts should be dissected free, ligated, and divided, but sizable ducts (especially when they are approximately the size of the cystic duct) should be assiduously preserved.

Goor and Ebert[10] repaired end-to-end over a T-tube a 2 mm aberrant right segmental duct imbedded, in part, in the wall of the gallbladder that had been severed during cholecystectomy. The patient's postoperative course was uneventful. Bile drainage from the T-tube was 100 to 150 cc per day in the repaired duct, and a postoperative cholangiogram was said to have demonstrated a patent anastomosis in this duct that drained a major portion of the right hepatic lobe.

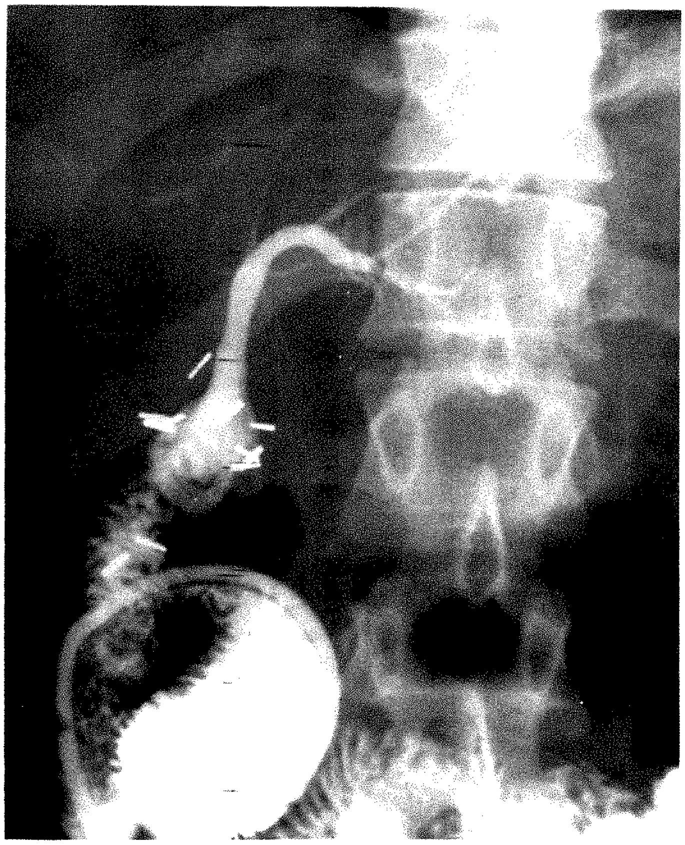


FIG. 4. Injection of dye into Roux-en-Y jejunal limb filling left hepatic duct system. There is no communication with right hepatic duct. Serum bilirubin returned to normal without further operation.

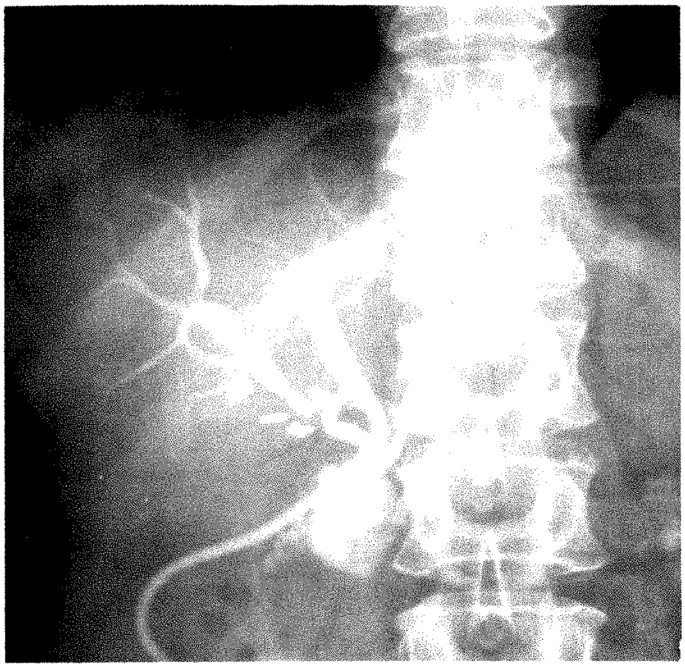


FIG. 5. Postoperative cholangiogram demonstrating T-tube in left hepatic duct and very low confluence of left and right hepatic ducts. Right hepatic duct (ventral-cranial segment) has been reanastomosed. Dorsal-caudal duct system not visualized.

A trying but eventually successful outcome was achieved by quite a different form of management reported by Pollock and Tabrisky[28] in an injury to a right anterior segmental duct. An unrecognized division of the duct during cholecystectomy led to a difficult postoperative course complicated by bile peritonitis that gradually cleared with drainage of the subhepatic space. Daily drainage of 800 cc from the severed right segmental duct during the first week steadily decreased to 250 cc per day by the fifth week and then ceased spontaneously without elevation of the bilirubin or other signs of biliary obstruction.

Three patients seen at the UCLA Hospital illustrate the manifestations of isolated injuries to a right segmental or lobar duct and the management of these lesions (Table 1).

Case 1 (E.K.): A 23-year-old woman had suffered right upper quadrant pain, jaundice, and fever 3 days after cholecystectomy performed on August 29, 1973. Two weeks later, a choledochojejunostomy Roux-en-Y was performed for obstruction of the common hepatic duct. The jaundice decreased, but the alkaline phosphatase continued to increase. A tube cholangiogram demonstrated good filling and drainage of the left hepatic duct but no visualization of the right hepatic ductal system (Fig. 4). On admission to the UCLA Hospital, her temperature was normal. There was no drainage from the right upper quadrant. The abdomen was soft, and there were active bowel sounds. Laboratory values were as follows: Prothrombin time was greater than 100%, hematocrit 29.3%, white blood cell count was 6500/mm,[3] total serum bilirubin 4.8 mg/100 ml, direct 4.2 mg/100 ml, SGOT 163 units, SGPT 245 units, protein 7.4 gm/100 ml, albumin 2.8 gm/100 ml, alkaline phosphatase 1,286 King-Armstrong (K-A) units. During a week of observation in the hospital, her condition remained stable, and results of hepatic function tests slowly improved. On October 30, 1973, 7 weeks after the left hepatic jejunostomy, the total serum bilirubin was 1.6 mg/100 ml and alkaline phosphatase was 574 K-A units. During the past year, she has led a normal life without further symptoms related to her biliary system.

Comment: Secondary reconstruction of the biliary system after cholecystectomy resulted in drainage of the left hepatic system only. As moderate jaundice readily receded and the patient was otherwise asymptomatic without evidence of infection, the decision was made to allow the right hepatic duct to remain obstructed in anticipation of atrophy of the right lobe and compensatory hypertrophy of left lobe.

Case 2 (W.E.): A 58-year-old woman had undergone a cholecystectomy on November 5, 1973, during which an anomalous right hepatic duct draining the cystic duct and joining the left hepatic duct at the level of the pancreas was divided. The right hepatic duct, which measured 3 mm in diameter, was repaired immediately in an end-to-end fashion. Postoperative cholangiograms (Fig. 5) through a T-tube placed in the long left hepatic duct demonstrated an area of constriction at the site of the anastomosis, with dye filling only the ventral-cranial segment of the right hepatic ductal system. Dye drained back slowly but adequately from this segment. The left ductal system was normal.

When seen at the UCLA Hospital on January 3, 1974, the patient had numerous minor complaints similar to those expressed before operation; however, she had maintained her weight, the stools were normal, and there was no history of jaundice, chills, or fever. *Proteus mirabilis* organisms were cultured from the bile. Laboratory values were as follows: Total protein, albumin, calcium, phosphorous, cholesterol, glucose, uric acid, creatinine, and lactic dehydrogenase (LDH) were within normal limits. The alkaline phosphatase was elevated to 128 units, the serum bilirubin to 1.7 mg/100 ml, and SGOT to 156 units.

Hematocrit was 39%, hemoglobin was 13.1 gm/100 ml, white blood cell count was 5900/mm,^{3} and urine was positive for bilirubin.

Despite the apparent defect in the right hepatic duct and the inability to demonstrate the dorsal-caudal segment of the right lobe on cholangiogram, it was elected to remove the T-tube and to observe her course. By January 20, 1974, the alkaline phosphatase had dropped to 41 units and the serum bilirubin to 0.3 mg/100 ml. She has remained well since that time.

Comment: Absence of the ducts of the right dorsal-caudal segment on the postoperative cholangiogram suggests that this duct had an anomalous, unrecognized course and that it was ligated and divided but not repaired. Although this patient had one segmental duct ligated and the lumen of another segmental duct compromised by a circumferential repair, minimal changes in hepatic function were demonstrated, and these had reverted to normal in less than 3 months. The anastomosis of a small bile duct, such as was done in this case, may well result in stricture, but if such occurs without infection, it will be without clinical symptoms. Therefore, the T-tube was removed promptly from the ductal system to prevent the exacerbation of the infection by a foreign body. Laboratory tests suggest that the anastomosis has functioned adequately to date.

Case 3 (A.A.): A 40-year-old woman had undergone cholecystectomy on January 7, 1971, at which time the common hepatic duct, which measured only 2-3 mm in diameter, was mistakenly identified as an accessory bile duct or a small blood vessel and divided. Upon proper recognition of the duct, it was reanastomosed over a small T-tube end-to-end to a diminutive (2 mm) common bile duct, one centimeter below the confluence of the left and right hepatic ducts. Due to a persistent extended drainage of large amounts of bile, acholic stools, and low grade fever, a second exploration was performed January 31, 1971, and a choledochojejunostomy was performed. Intermittent attacks of jaundice and cholangitis persisted until her admission to the UCLA Hospital on May 1, 1971. At reexploration 2 days later, the stenosed choledochojejunal anastomosis was resected, and the common hepatic duct was anastomosed to a Roux-en-Y limb fashioned out of the jejunal loop. Of interest, however, during the dissection was the identification of a 3 mm bile-containing duct opening into the right lobe of the liver dorsal to the hepatoduodenal ligament. X-ray studies made after the injection of dye into this duct demonstrated the ductal system of the dorsal-caudal segment of the right lobe (Fig. 6A). A cholangiogram made by injection of dye through a catheter in the common hepatic duct demonstrated the left hepatic duct and the ventral-cranial segment of the right lobe (Fig. 6B). Fearing that a separate anastomosis of this small duct to the jejunum might become stenotic and infected and as there was no evidence of infection in the segment at this time, the decision was made to ligate the duct and to allow the segment to atrophy.

External bile drainage of approximately 300 cc per day from the site of the ligated duct began 1 week after operation and continued for 3 weeks before ceasing spontaneously. The serum bilirubin which was 9 mg/100 ml before operation, rose to 14.4 mg/100 ml the day after operation, decreased to 5.0 mg/100 ml 2 weeks after operation, and returned to normal levels 3 weeks later. The SGOT, which was 78 units prior to operation, rose to a high of 130 units the day after operation and fell to 51 at the time of discharge from the hospital. The alkaline phosphatase, which was 22.5 K-A units prior to operation, fluctuated between 15 and 22, falling to 15.5 K-A units at the time of discharge. In the 3½ years since the duct anastomosis was revised and the external bile fistula closed spontaneously, the patient has been well.

Comment: The anomalous arrangement of the ducts with an unusually small extrahepatic ductal system and an aberrant segmental duct led to an inadvertent division of the common hepatic duct. The third repair with a choledochojejunostomy has functioned satisfactorily for 3½ years. A biliary fistula, which developed from the aberrant segmental duct despite a careful pursestring suture ligation, closed spontaneously, as expected, after draining approximately 300 cc per day for 5 weeks. Closure of the duct and subsequent atrophy of the segment was the course of management selected rather than reanastomosis. Adequate drainage should be provided when such ducts are ligated since necrosis of the end of the ligated duct with subsequent bile leakage is not uncommon. An anastomosis of this small duct to the jejunum might well have become stenotic, and had the ductal system become chronically infected behind the stenosis, resection of the liver

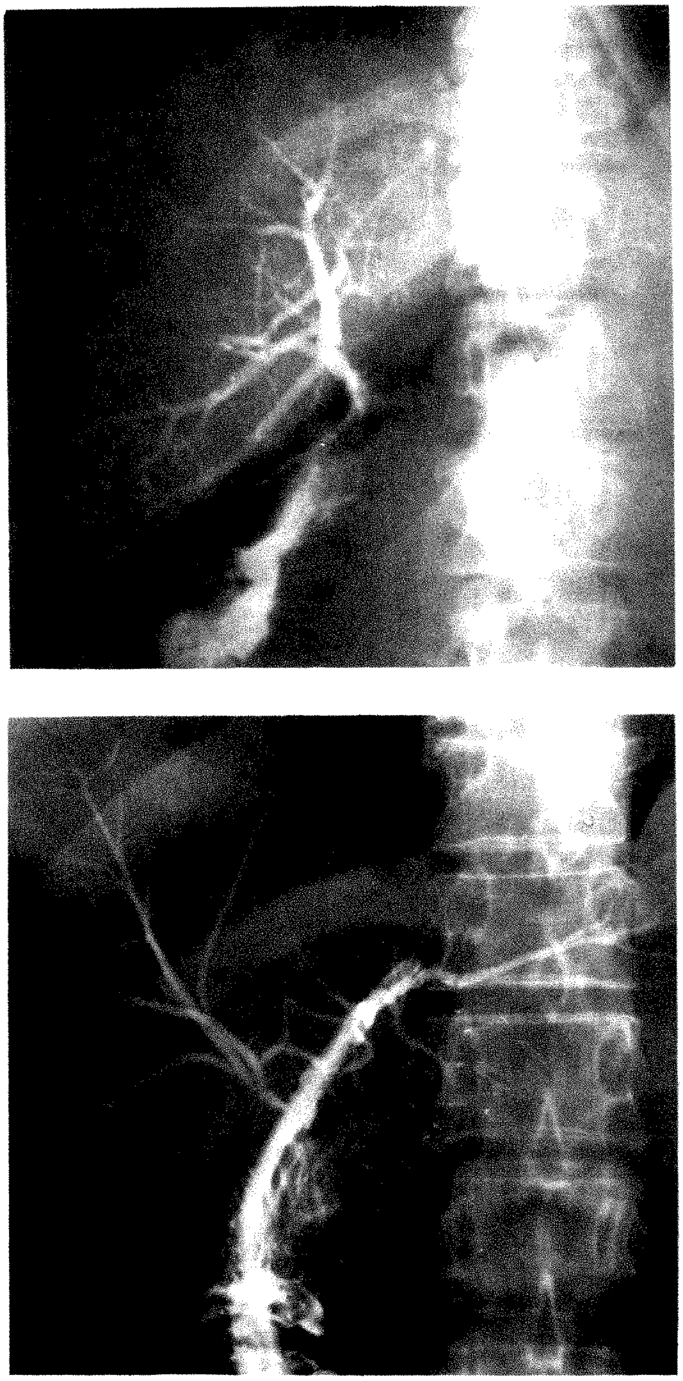


FIG. 6. (Patient A.A.) *A*, Dye injection at operation into right segmental duct visualized dorsal-caudal segment of right lobe. Duct was ligated. *B*, Dye injection via catheter after anastomosis of common hepatic duct to Roux-en-Y jejunal limb visualized left hepatic and right ventral-cranial segment duct systems.

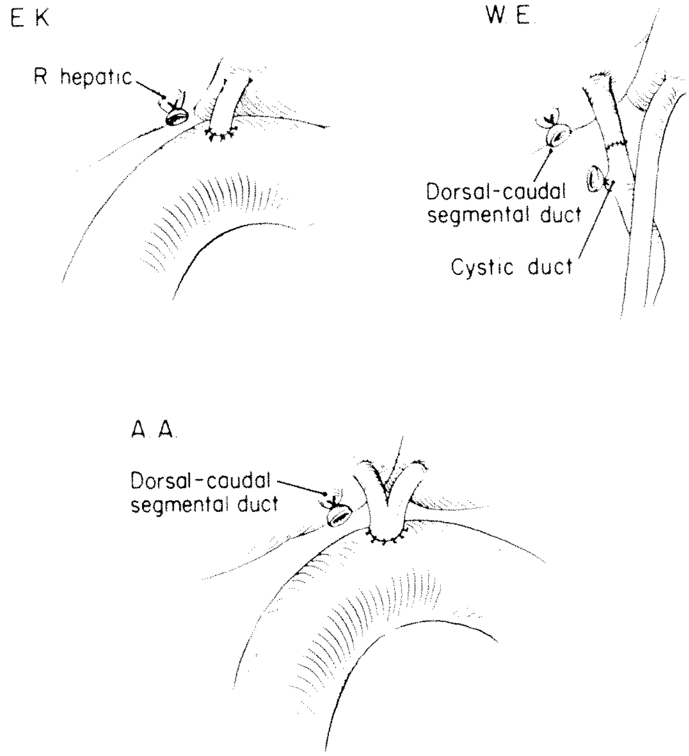


FIG. 7. Diagrammatic summary of three patients with injuries of segmental or lobar hepatic ducts.

segment might have been required to eradicate the intrahepatic infection.

Discussion

Segmental or hepatic bile duct injury without infection.

In at least two patients (Fig. 7), a confusing anomalous arrangement of the extrahepatic ductal system with an aberrant right segmental hepatic duct led to inadvertent ductal injury. In both patients, a right dorsal-caudal segmental duct was ligated, with temporary external biliary fistula in one but with eventual healing and normal liver function in both. As there was no external drainage or infection, no further attempt was made to treat the moderate constriction at the site of end-to-end repair in the right ventral-cranial segmental duct of one patient (W.E.).

In the first patient (E.K.), normal liver function was regained, and she was clinically well 6 weeks after an hepaticojejunostomy which restored bile flow only from the left hepatic duct.

These cases demonstrate that complete obstruction of one-quarter to one-half of the biliary drainage system is quite well tolerated as long as there is no external bile fistula or cholangitis and as long as the drained hepatic parenchyma has essentially normal function. The initial and postoperative management of patients with segmental or lobar hepatic duct injury is outlined in Table 2.

Segmental or Hepatic Bile Duct Injury With Infection

Persistent partial stenosis of an injured segmental or lobar hepatic duct, particularly if the duct has been anastomosed to the alimentary tract, invariably leads to bile stasis, sludging, infection, and bouts of clinical cholangitis with fever, pain, jaundice, and eventual reoperation. Dilatation and thickening of the wall of the duct may permit a more accurate reconstruction at the second operation than was possible at the first, and if adequate unobstructed biliary flow can be reestablished through the duct, the infection will be eliminated. On the other hand, if the cholangitic infection persists behind a partially obstructed duct, infected duct saccules and parenchymal abscesses develop, and an appropriate hepatic resection usually will be required to eradicate the infection.

High strictures that involve the confluence of the hepatic ducts require individual reconstruction of the left and right hepatic ducts. The right side has a particular proclivity to persistent stenosis because the right duct bifurcates within a short distance above the confluence into its smaller branches. Its very short extrahepatic course makes it technically difficult to create a satisfactory biliary-enteric anastomosis. Therefore, intrahepatic abscesses are most likely to occur in the right lobe in patients with long-standing obstruction and infection (Table 3).

Case 1 (A.O.): A 47-year-old woman gave a history of repeated bouts of biliary obstruction and cholangitis following a cholecystectomy in 1949. In January, 1966, a stone was said to have been removed from her common duct. An external biliary fistula and repeated subphrenic abscesses which developed postoperatively were demonstrated to communicate with the right intrahepatic biliary system. A stricture that involved the confluence of the hepatic ducts was treated in June, 1966, by anastomosis of the right and left hepatic ducts individually to a Roux-en Y jejunal limb. Two further right subphrenic abscesses occurred, one of which developed into a biliary bronchopleural fistula, and a right hepatectomy was performed on October 30, 1967. The left hepatic duct, which was fibrotic and narrowed, was reanastomosed to the jejunum; however, the patient died from hepatic failure shortly after the operation. The resected lobe contained a 6 x 4 x 4 cm abscess with other microscopic abscesses, centrolobular hepatic necrosis and atrophy, fibrosis, and regenerating liver tissue.

Comment: The long-standing obstruction and infection led to intrahepatic abscesses with rupture into the subphrenic space. Hepaticojejunostomy was ineffective in eradicating the infection. Ad-

TABLE 2. *Segmental or Hepatic Bile Duct Injury Without Infection*

Initial Management	
Ligate small segmental ducts <1 mm	
End-to-end repair of larger segmental and hepatic ducts >2 mm	
Drainage and antibiotics	
Management After Repair of Duct	
Good function	No further treatment
Asymptomatic stenosis	No further treatment
Stenosis with infection	Reoperation to establish adequate biliary-enteric drainage

TABLE 3. *Segmental or Hepatic Bile Duct Injury With Infection*

Patient	Cause	Duct Injured	Treatment	Result	Remarks
A.O.	Cholecystectomy secondary repair	R. and common hepatic	Partial R. hepatic lobectomy. L. hepatico-jejunostomy	Died	Generalized intra-hepatic biliary sclerosis
R.B.	Bullet wound	R. hepatic	R. hepatic lobectomy	Well	R. hepatic artery severed. Chronic draining abscess, R.
S.W.	Sclerosing solution in Echinococcus cyst	R. and common hepatic	Partial R. hepatic lobectomy. L. hepatico-jejunostomy	Well	Persistent R. sub-phrenic biliary abscess

vanced biliary sclerosis and secondary cirrhosis led to hepatic failure after an exceedingly difficult right hepatic lobectomy. A successful lobectomy might have been possible had the diagnosis of the intrahepatic abscess been made some months earlier before the extensive perihepatic scarring and the biliary sclerosis developed.

Chronic intrahepatic abscesses that communicate with a damaged biliary system may arise in association with other types of trauma, as illustrated by the following cases.

Case 2 (R.B.): A 23-year-old army sergeant suffered a shrapnel wound June 20, 1973, that severed the right hepatic duct and artery and penetrated the right lobe of the liver. A right subphrenic abscess developed that communicated freely with the right intrahepatic biliary system and a biliary fistula from the hilus of the liver (Fig. 8). Recurrent abscesses, jaundice, biliary drainage, and repeated bleeding continued until a right hepatectomy and end-to-end anastomosis of the left hepatic duct to the common duct was performed on September 24, 1973. The patient recovered completely after a 2½-month hospitalization.

Comment: Despite repeated drainage of subphrenic and intrahepatic abscesses, the infection could not be controlled because of interference with bile drainage at the hilus. Removal of the infected right lobe and repair of the left ductal system eradicated the infection and biliary drainage and restored normal liver function.

Case 3 (S.W.): An 11-year-old girl had had a repeat evacuation of a right hepatic echinococcus cyst and injection of a sclerosing solution into the cavity when she was 6 years old. Apparently, the cyst cavity communicated with her right ductal system, for a stenosis of the right and common hepatic ducts developed. Infected bile repeatedly accumulated in the cyst cavity and in the right subphrenic space, requiring numerous drainage procedures. When she was 7½ years old, evacuation of an intrahepatic abscess and anastomosis of a Roux-en-Y jejunal limb to the opening of the bile fistula on the dome of the right lobe relieved the recurrent subphrenic abscesses; however, repeated bouts of cholangitis continued during the next 3½ years, leading to portal hypertension, splenomegaly, and esophageal varices. At the time of her last admission, the enlarged spleen was removed and an end-to-side splenorenal shunt performed. A part of the severely atrophied right lobe was removed, and a hepaticojejunostomy was performed between the Roux-en-Y limb and the markedly dilated left hepatic duct (Fig. 9). She has developed normally and has been well during the 4 years since the last operation.

Comment: A partially successful attempt was made to drain a blocked right biliary system and intrahepatic abscess into a peripherally placed Roux-en-Y limb. The portal hypertension could have been averted and the course of the prolonged repeated infections abbreviated had the infected right lobe been more promptly removed and the partially obstructed left hepatic duct decompressed.

Segmental or hepatic bile duct injury with infection

In patients with chronic biliary obstruction, infection within the biliary system (cholangitis) will invariably develop above the point of stenosis, and adequate repair of the stenotic area will relieve the infection. However, if the obstruction is also associated with an intrahepatic abscess, resection of the appropriate liver lobe and repair of the remaining ductal system are usually necessary to control the infection.

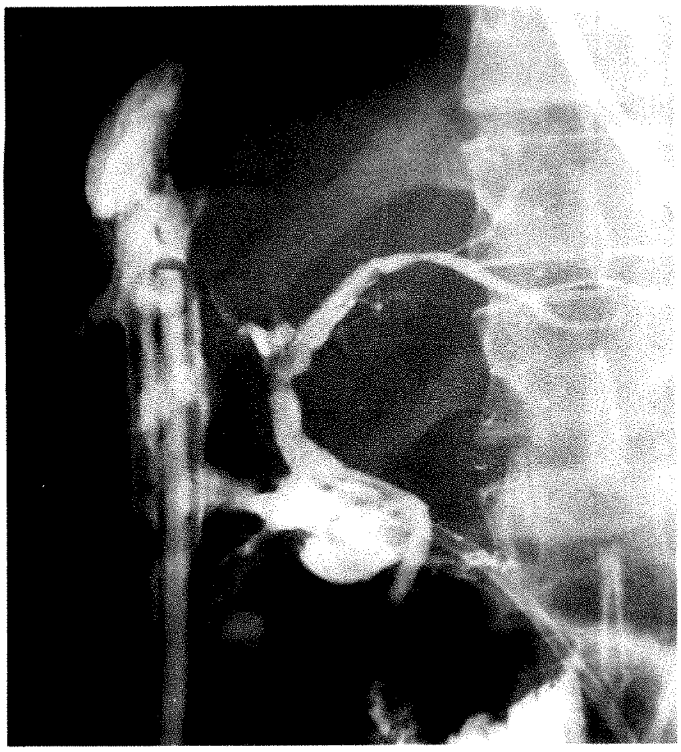


FIG. 8. Injection of dye through tube in left hepatic duct demonstrating leakage through disrupted right duct system into intrahepatic abscess in right lobe and right subphrenic space.

TABLE 4. *Congenital Ductual Lesions*

Patient	Duct Involved	Symptoms	Treatment	Result
R.M.	L. hepatic	Recurrent fever, jaundice, pain	Choledocho-jejunostomy. Drainage of cyst	Well
T.G.	L. hepatic	Recurrent fever, jaundice, pain	Hepatico-jejunostomy	Well
C.H.	Diffuse cystic dilatations	Recurrent fever, jaundice, pain	Hepatico-jejunostomy. Indwelling tube	Improved
L.B.	L. intra-hepatic	Fever, jaundice	L. hepatectomy	Well
F.K.	R. intra-hepatic	Fever	R. hepatectomy	Died
S.C.	Ventral-cranial segment R.	Fever, pain	R. hepatectomy	Well

Congenital Lesions

A variety of congenital anomalies of the lumen of the normally arranged segmental or lobar ducts may occur. These include single isolated lesions, multiple anomalous conditions, and diffusely involved ductal systems. Idiopathic hepatic lobar or segmental atrophy[33] may be the result of congenital atresia of a lobar or segmental duct such as was seen in two of our patients. As incidental findings, the left lobe in one and the left lateral segment in another were atrophic. The congenital lesions that usually confront surgeons are related to some type of ductal dilatation with stasis of bile flow, precipitation of solid material, and infection. Clinically, such patients usually show signs of infection in the presence of jaundice so that the biliary system is immediately suspect. When the process is confined to a segment of the intrahepatic ductal system, jaundice is absent, and early localization of the source of a systemic infection may be difficult. The following six patient reports illustrate various types of congenital hepatic duct lesions (Table 4).

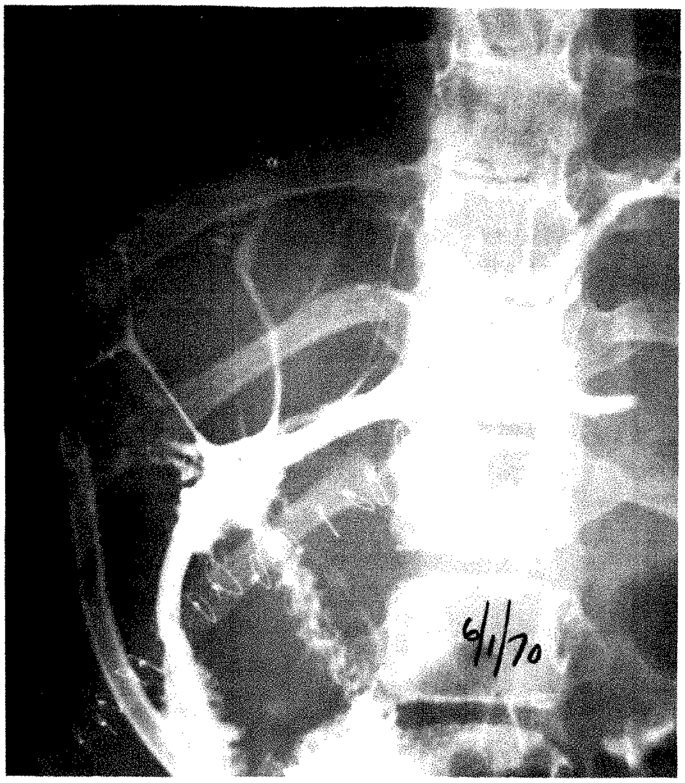


FIG. 9. Dye injected via tube through common hepatic jejunal anastomosis. Note enlargement of left duct system and marked atrophy of remaining portion of right intrahepatic ducts.

Cases 1 and 2 (R.M. and T.G.): These two patients, previously reported upon,[17] had isolated cystic dilatations of the left hepatic duct, a site in the ductal system that seems to have a predilection for such anomalies. Glenn and Moody[9] have described patients with similarly located cystic lesions. In both patients, soft pigment stones and sludge collected in the saccular dilatation, causing repeated bouts of jaundice and cholangitis. In one patient (T.G.), the cystic dilatation was located at the hilus outside of the liver, and adequate drainage of the cyst and relief of symptoms were obtained by anastomosis of the biliary cyst to a Roux-en-Y jejunal limb. In the second patient (R.M.), the cyst was intrahepatic, making treatment more complicated. The infection was finally controlled by placement of an indwelling catheter into the cyst for prolonged daily irrigations, and a Roux-en-Y jejunal limb was anastomosed end-to-end to the dilated common hepatic duct so that biliary debris could pass readily into the alimentary tract.

Multiple intrahepatic cystic dilatations of the biliary tract may be diffuse throughout the system or confined to an anatomical segment of the liver.

Case 3 (C.H.): An 18-year-old girl had biliary symptoms since a choledochal cyst was anastomosed to the duodenum when she was 1 year old. In association with the choledochal cyst, she had diffuse cystic dilatation throughout the intrahepatic ductal system (Caroli's disease) (Fig. 10). After 6 operations for repeated attacks of cholangitis, she now has a high hepaticojejunostomy. An external tube which passes into the dilated hepatic duct has been left in place for approximately 2 years to allow access to the ductal system for irrigation and instrumentation of the sludge and debris that form in the dilated ducts. She has been free of cholangitis during this period.

Because of the diffuse distribution of the cystic areas throughout both lobes of the liver, the treatment in such cases must be directed toward keeping the biliary system as free as possible of particulate matter by irrigations, leaving as large a communication as possible between the biliary and enteric tracts. In some patients with a history of frequent recurring episodes of cholangitis, a route of access should be provided to the biliary tree for periodic mechanical removal of stones and sludge.

Multiple cystic dilatations of the intrahepatic ducts were localized to resectable anatomical segments of the liver in the following three cases. The left lobe was affected in one patient, the right lobe in the second, and the right ventral-cranial segment in the third. It is remarkable that, although these malformations were congenital and had been present since birth, they did not become symptomatic until the patients were 46, 41, and 16 years of age.

Case 4 (L.B.): A 47-year-old woman with cystic malformations confined to the left lobe had had symptoms of increasingly severe attacks of cholangitis for 1½ years. During an acute febrile episode with gram negative sepsis, the patient underwent drainage of what was thought to be a large left hepatic abscess. Subsequent x-ray studies indicated that the abscess was a part of a markedly dilated left hepatic ductal system with numerous large cystic areas. With external drainage, the acute episode was relieved, but attacks of cholangitis persisted until the left lobe was resected. After recovery from an extensive wound infection, the patient remained well (Figs. 11a and b).

Case 5 (R.K.): A 51-year-old man, mentioned in a previous report,[17] had a 10-year history of recurrent cholangitis. He underwent a choledochojejunal anastomosis to control a continued biliary sepsis. When the operation proved to be totally ineffective, a right hepatectomy was performed, but the patient died of overwhelming sepsis. Three large cystic areas tightly packed with bilirubinate stones served as the nidus to perpetuate his cholangitis. Had these areas all been located and drained and the active acute infection allowed to subside prior to the hepatectomy, a successful outcome might have been achieved.

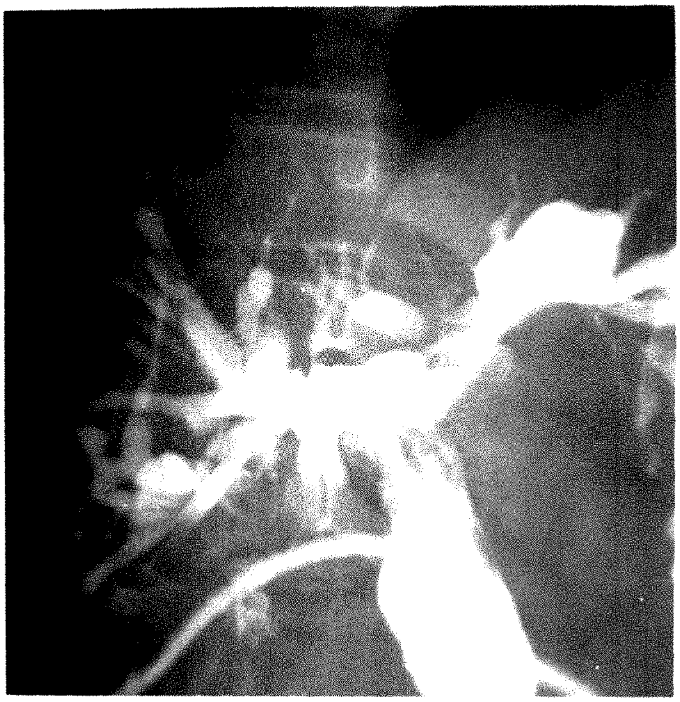
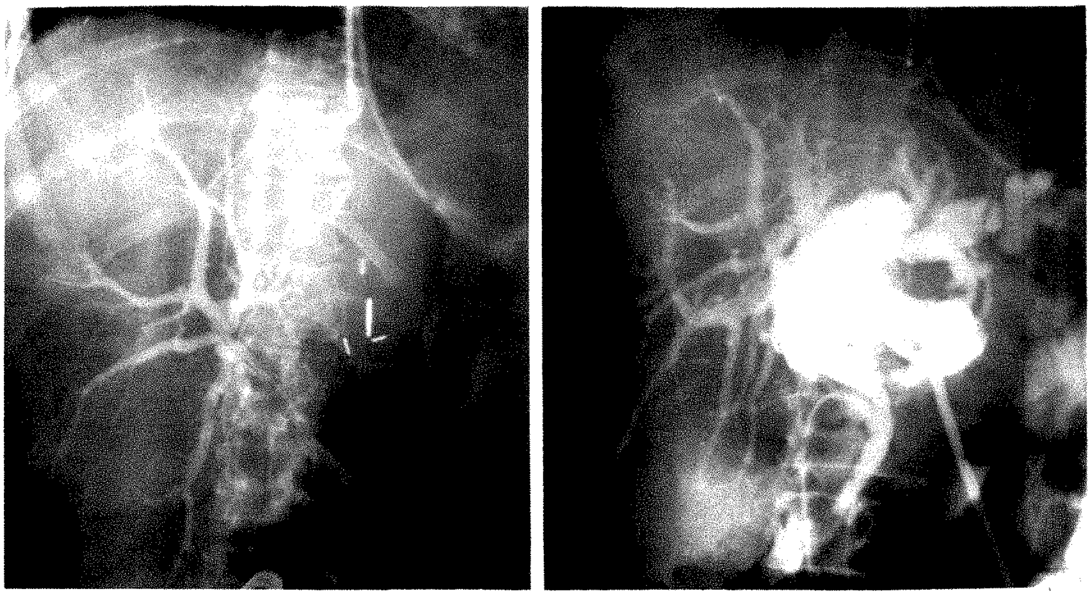
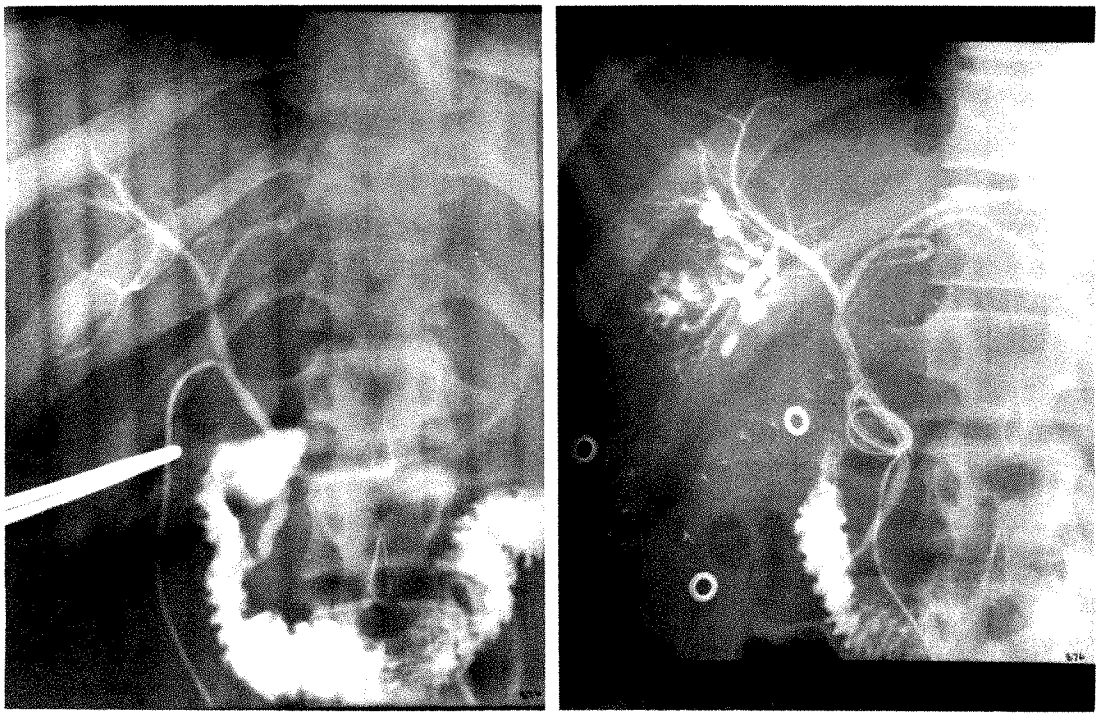


FIG. 10. Tube cholangiogram of patient with anastomosis of jejunum to markedly dilated hepatic duct after partial excision of congenital choledochal cyst. Multiple cystic dilatations of the entire intrahepatic biliary system are demonstrated.

Case 6 (S.C.): A very puzzling diagnostic problem was presented by a 16-year-old boy who was admitted to the UCLA Hospital with a 10-day history of abdominal pain with chills and fever for 5 days. Attention was directed to his biliary system by increased tenderness in the right upper quadrant and a total serum bilirubin of 2.3 mg/100 ml. *Escherichia coli* bacteria were cultured in the blood. Findings on liver scan were normal. At operation, the gallbladder was distended and thick-walled, as was the common bile duct, but no stones were present. The bile was dark, but no particulate matter was seen. An operative cholangiogram, which visualized the intra- and extrahepatic biliary system, was interpreted as normal (Fig. 12a). The liver and spleen were enlarged, and the portal pressure was 212 mm of saline. The gallbladder was removed and a T-tube placed in the common duct. Postoperatively, his febrile course continued unabated. The serum bilirubin rose to 3.8 mg/100 ml, alkaline phosphatase to 128 units, SGOT to 220 units, and SGPT to 154 units. A postoperative cholangiogram demonstrated multiple cystic collections of contrast agent in the dorsal-caudal segment of the right hepatic biliary system (Fig. 12b). A partial right hepatectomy removed a segment of liver containing multiple *Escherichia coli* abscesses in the biliary tree. Since the postoperative period, he has been well for 1½ years.



FIGS. 11A and B (left), Demonstration of marked saccular dilatation of left intrahepatic system. Right intrahepatic ducts are normal. (right) Normal right intrahepatic ducts after resection of left lobe.



FIGS. 12A and B. (left). Operative cholangiogram interpreted as normal. Note that dorsal-caudal segment of right lobe is not visualized. (right) Postoperative cholangiogram demonstrated multiple infected cystic areas in dorsal-caudal segment of right lobe.

Congenital lesions

Single localized cystic dilatations in the major hepatic ducts can be drained into the alimentary tract. When infection and cholangitis supervene in the patient with multiple diffusely situated intrahepatic cystic dilatations, surgical treatment is not curative, but palliation may be achieved by hepaticojejunostomy, with or without an indwelling catheter. Localized infected cystic dilatations of the intrahepatic ducts may be resected by segmental or lobar hepatectomy. When acute sepsis is present, antibiotic therapy and biliary drainage or drainage of a dominant intrahepatic abscess should be instituted before definitive hepatic resection is undertaken (Table 5).

Intrahepatic Stones

Intrahepatic stones occur in one of two conditions. The most common is the patient with a diffuse dilatation of the ductal system secondary to the long continued presence of multiple common duct stones associated with chronic cholecystitis and cholecystolithiasis. Great care should be taken in such cases to insure the removal of all stones. Repeated x-ray studies of good quality are essential in order to evaluate the completeness of stone removal. The choledochoscope may also be of value in locating concealed stones. In patients with a markedly dilated, thick-walled common duct, the creation of a lateral choledochoduodenostomy should be considered as a prophylactic measure against retained or recurrent common duct stones.

Intrahepatic stones that serve as a nidus of continued infection and repeated attacks of cholangitis that cannot be removed by the usual methods with scoops, forceps, Fogarty catheters, wire baskets, or the aid of the choledochoscope may require hepatic resection. On the other hand, the mere presence of an intrahepatic stone unassociated with any clinical symptoms of biliary tract disease is not necessarily an indication for remedial surgical procedures, but such patients should be maintained under observation. The initial treatment to be used for the irremovable symptomatic intrahepatic stone, however, is a choledochoenteric anastomosis. If such proves to be ineffective in relieving the symptoms, hepatic resection must be considered, as illustrated by the following cases (Table 6).

Case 1 (S.B.): A 43-year-old woman had suffered with intermittent epigastric and right upper quadrant pain for 25 years. A cholecystectomy in 1945 had relieved her symptoms for 7 years. Recurrent common duct stones were removed at operations in 1953, 1955, and 1963. T-tube cholangiograms showed a stricture of the left intrahepatic duct with multiple stones distal to the stenotic area. In October, 1963, the left lateral segment of the liver was excised, including the stenotic hepatic duct and distal stones. The patient has had subsequent attacks of pancreatitis but no further biliary tract difficulty.

Comment: It seems quite likely that the post-stenotic infection and

TABLE 5. *Congenital Hepatic and Intrahepatic Ductal Lesions With Infection*

Condition	Treatment
Single lesion involving major hepatic duct	Cyst-jejunal anastomosis
Multiple intrahepatic cysts	
Diffuse	Hepaticojejunostomy
Localized	Hepatic resection

TABLE 6. *Intrahepatic Stones*

Patient	Duct	Disease	Symptoms	Treatment	Result
S.B.	L. intrahepatic	Congenital	Cholangitis	L. lateral segmental resection	Well
A.B.	L. intrahepatic	Retained stone	None	Attempted extraction	Well?

debris in the left hepatic duct were passed into the common duct, producing attacks of cholangitis and right upper quadrant pain. The marked deformity made an intraductal approach to the stones impossible. Hepatic resection was the only way whereby the stones and the infected duct could be removed.

Case 2 (A.B.): This 58-year-old woman illustrates, in contrast, the possible innocuous nature of an intrahepatic stone. The patient became jaundiced and febrile in December, 1972, and a chronically inflamed gallbladder with stones was removed on January 4, 1973. Multiple stones were removed from a grossly dilated extra- and intrahepatic ductal system. A postoperative T-tube cholangiogram demonstrated a 1½ cm retained stone in one of the major left intrahepatic biliary ducts (Fig. 13). The system was otherwise negative. Attempts to remove the stone by manipulation via the T-tube tract were unsuccessful.

Comment: As the patient is entirely asymptomatic with normal liver function tests, she has been treated conservatively since that time. If such a patient becomes symptomatic, operative removal of the stone would be attempted with the aid of the choledochoscope, and a direct approach to the left hepatic duct would be performed in conjunction with choledochoduodenostomy. If this were unsuccessful and attacks of cholangitis persisted without other explanation, hepatic resection would be considered.

Intrahepatic stones

At the initial operation in cases of primary (congenital) or secondary (acquired) dilatation of the ductal system with multiple calculi, it is important that every effort be made to extract all stones from the intra- and extrahepatic systems with all of the usual techniques. Carefully performed post-exploratory operative cholangiograms should demonstrate the major intrahepatic segmental ducts. Choledochoenteric anastomosis should always be performed when the duct dilatation is primary and seriously considered for the patient with long-standing multiple calculous disease with marked secondary duct thickening and dilatation. Hepatic resection may be required for the irremovable intrahepatic stone with distal infection. Some stones of this type are remarkably well tolerated and generally require treatment only when they become symptomatic.

Hepatic Duct Carcinoma

In a previous study of carcinoma of the extrahepatic biliary tract, we found the confluence of the hepatic ducts at the hilus of the liver to be involved in 34 of 63 cases.[18] Resection of the tumor with duct enteric anastomosis was possible in only four patients. Major hepatic resection combined with excision of the tumor was used in two additional patients. A T-tube was inserted into the common duct and through the site of tumor obstruction in 13 patients, and in three others, an enteric anastomosis to the hepatic ducts above the obstruction was used as a palliative procedure. Palliation was considered good in 5, fair in 7, and poor in 4 patients. When a tube was inserted through an area of malignant obstruction or through a duct enteric anastomosis into the intrahepatic system, it usually passed into either the right or left hepatic system. The extent of biliary drainage from the opposite lobe varied from complete drainage to complete obstruction. With either extreme, the result seemed to be better than with partial drainage, particularly if infection were present. The following four cases are illustrative (Table 7).

Case 1 (L.D.): A 65-year-old man was admitted to the UCLA Hospital with signs of increasing renal dysfunction 2½ weeks after cholecystectomy and insertion of a small T-tube through a stenotic area in the common bile duct. Jaundice, pruritis, and weakness had been present for 3 months preoperatively. After operation, his serum bilirubin fell from 21 to 7.5 mg/100 ml where it remained. The serum creatinine rose to 4.0 mg/100 ml. A T-tube cholangiogram demonstrated the tube to be in the right hepatic duct with marked dilatation of the entire right intrahepatic ductal system above a site of complete obstruction at the confluence of the hepatic ducts (Fig. 14). At reoperation, a Roux-en-Y jejunal limb was anastomosed to the site of confluence of the left and right hepatic ducts above the tumor obstruction as a palliative bypass.

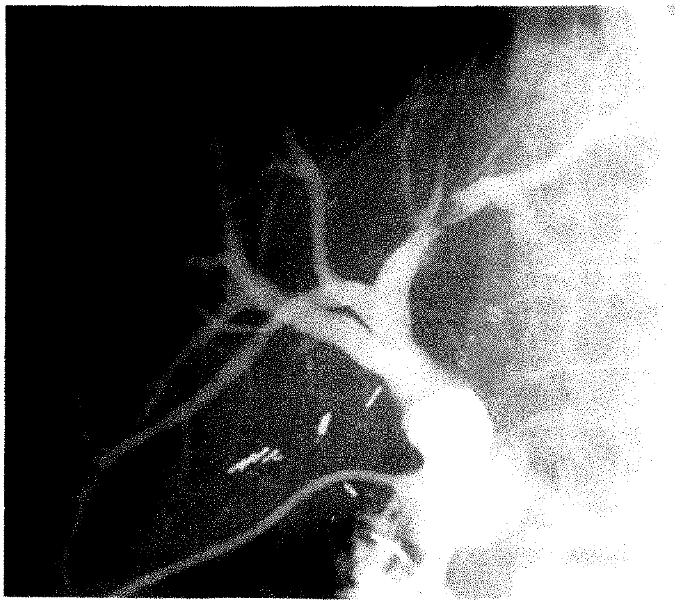


FIG. 13. Cholangiogram demonstrating an intrahepatic stone in the main branch of the left hepatic duct. The patient has been asymptomatic for more than 2 years.

TABLE 7. *Hepatic Duct Carcinoma*

Patient	Location Tumor	Intrahepatic System Drained	Procedure	Result
L.D.	Confluence hepatic ducts	1st operation R., partial L. 2nd operation R. and L.	T-tube through tumor Hepaticojejunostomy	Bilirubin ↓ 7.5 Bilirubin normal. Lived 11 mo
C.F.	Confluence hepatic ducts	L.	L. hepatico-duodenostomy	Bilirubin, alkaline phosphatase normal, 2½ mo. after operation until death at 1 yr
H.C.	Confluence hepatic ducts. Extension into L. hepatic duct.	R.	T-tube through tumor into R. hepatic duct	Bilirubin normal, alkaline phosphatase elevated, 3 mo after operation
E.Z.	Confluence hepatic ducts	R. ventral-cranial segment-partial?	T-tube through tumor	Bilirubin ↓ 6-7 4 mo

The serum bilirubin returned to normal 4 weeks after operation and remained so until shortly before he died 11 months after operation.

Comment: Although there was some communication of the left and right intrahepatic ductal systems, as demonstrated on cholangiogram, the decompression of the system was not adequate through the T-tube limb in the right duct to decrease the ductal dilatation or to lower the serum bilirubin below 7.5 mg/100 ml. Adequate drainage of both lobes via a hepaticojejunostomy above the tumor returned the serum bilirubin to normal.

Case 2 (C.F.): A 54-year-old man had a T-tube inserted into the common duct below a point of obstruction after about a month of jaundice and abdominal discomfort. On the basis that the scarred common duct blockage might be sclerosing cholangitis, he was treated with Prednisone over the ensuing 2 months with some apparent temporary relief of his symptoms. At reoperation, a carcinoma at the confluence of the hepatic ducts extending into the right lobe was identified, and the left hepatic duct was anastomosed to the duodenum (Fig. 15). Over the next 2½ weeks prior to discharge from the hospital, the serum bilirubin fell from 25.3 mg/100 ml to 5.1 mg/100 ml and alkaline phosphatase from 86.4 to 25.3 k-A units. Two weeks later, the stool and urine were of normal color.

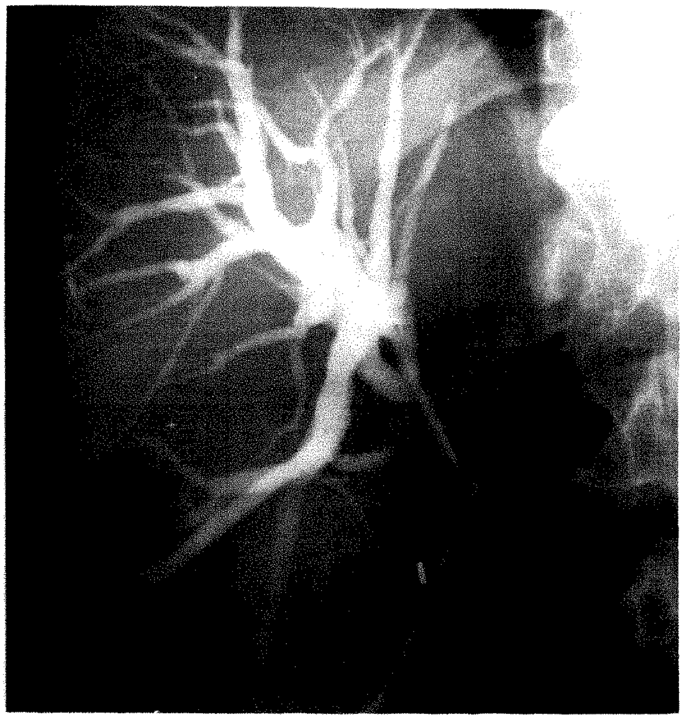


FIG. 14. Small T-tube placed through an obstructing carcinoma at the confluence of the hepatic ducts into the dilated right hepatic system was too small to provide adequate drainage.

The alkaline phosphatase and serum bilirubin were normal 2½ months after operation and remained so until the patient died of bleeding associated with tumor erosion of the gastric wall 1 year after operation.

Comment: This patient's course demonstrates that free drainage of one normal hepatic lobe (the left in this case) despite complete obstruction of the ductal system of the other lobe is adequate to bring about a normal serum bilirubin and alkaline phosphatase within 2 months after the relief of complete biliary obstruction.

Case 3 (H.C.): In this 46-year-old woman, operation in February, 1974, disclosed an obstruction of the bile ducts at the confluence of the hepatic ducts with marked dilatation of the intrahepatic ductal system above this level. After dilatation of the obstruction and insertion of a T-tube, there was drainage of bile for approximately 1 month, after which drainage ceased and the tube was removed. The jaundice increased, and she lost 20 pounds before her admission to UCLA and the second exploration on July 24, 1974. Carcinoma of the confluence of the bile ducts was found with extension of the tumor up the left hepatic duct. The lumen of the obstructed duct was dilated, and a T-tube was inserted through the obstruction into the right hepatic duct (Fig. 16). Three months after operation, the serum bilirubin was 1.2 mg/100 ml, and the serum alkaline phosphatase was 475 K-A units. Six months after operation, the patient had returned to work. The serum bilirubin was 0.9 mg/100 ml, the alkaline phosphatase 406 units, and the SGOT 137 units. X-ray studies demonstrated good filling and emptying of the right hepatic ductal system. The left system was completely obstructed.

Comment: In this case, there is free drainage of the right hepatic ductal system with complete uninfected obstruction of the left hepatic duct. Serum bilirubin levels came down to normal in 3 months and have remained so. The alkaline phosphatase is still elevated. The patient is symptomatically well.

Case 4 (E.Z.): A 40-year-old man was admitted to the hospital on August 26, 1974, with a 2-month history of upper abdominal pain and deepening jaundice. At operation on September 9, 1974, a T-tube was placed through a fibrotic obstruction of the common hepatic duct up into the right hepatic ductal system. His serum bilirubin, which was

21.5 mg/100 ml at the time of operation, dropped to 10.8 mg/100 ml, and the alkaline phosphatase fell from 117 units to 73 units (normal 15-45) at the time of discharge 11 days after operation. Postoperative T-tube cholangiograms showed the proximal limb of the T-tube to extend well out into a tertiary segment of the right ductal system with filling of about one-half of the ducts in the ventral-cranial segment. There was no evidence of drainage about the catheter or of filling of the ducts in the left lobe or the dorsal-caudal segment of the right lobe. During the ensuing 4 months since operation, the bilirubin has ranged from 6 to 7 mg/100 ml, the alkaline phosphatase about 390 K-A units, and there has been one episode of intermittent low-grade fever of 100 F. Pseudomonas and another gram negative rod were grown in cultures of the bile. Despite the icterus, the patient has felt well, maintained his weight, and remained asymptomatic. A repeat T-tube cholangiogram on November 27, 1974, showed a decrease in the size of the ducts in the portion of the system that had been drained (Fig. 17). Again, only a portion of the ductal system of the ventral-cranial segment was demonstrated. No ducts were seen in the left lobe or in the dorsal-caudal segment of the right lobe.

Comment: The operative findings and cholangiographic studies would indicate that the present T-tube is probably draining less than one-quarter of the hepatic mass, and cultures demonstrate the presence of infection. If the patient should survive a sufficient period of time, it is possible that adequate hyperplasia would occur in the drained area to restore normal liver function. At present, the persistent serum bilirubin of 6 to 7 mg/100 ml indicates that that portion of the biliary system being drained is insufficient to excrete an adequate amount of bilirubin and to maintain a normal serum bilirubin level.

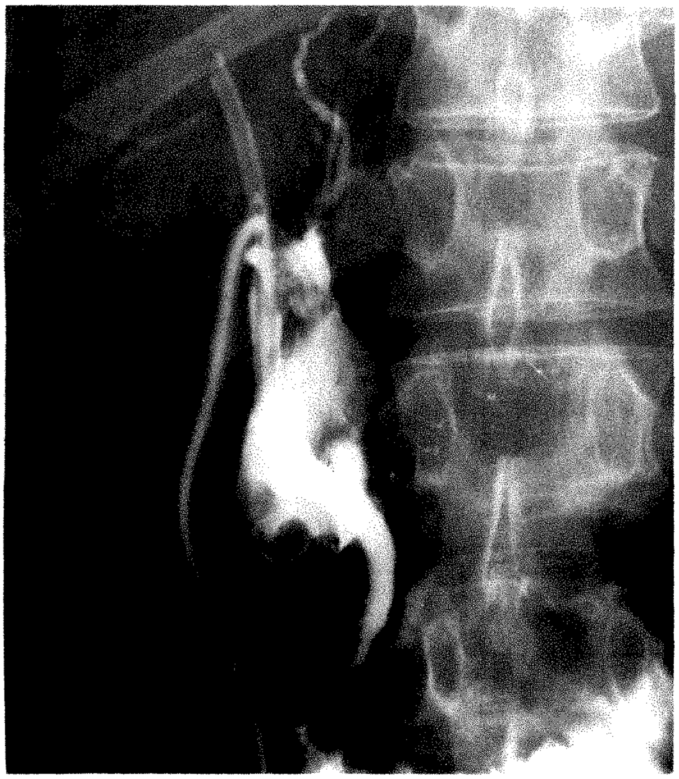


FIG. 15. Attempted passage of T-tube through the obstructing carcinoma of the right hepatic duct; the duodenum has been anastomosed to the left hepatic duct. Dye injected via the T-tube demonstrating that tube does not pass above the tumor and that the right duct is completely obstructed. The dye, however, passes down the common duct into the duodenum and refluxes through the hepaticoduodenostomy into the left hepatic duct.

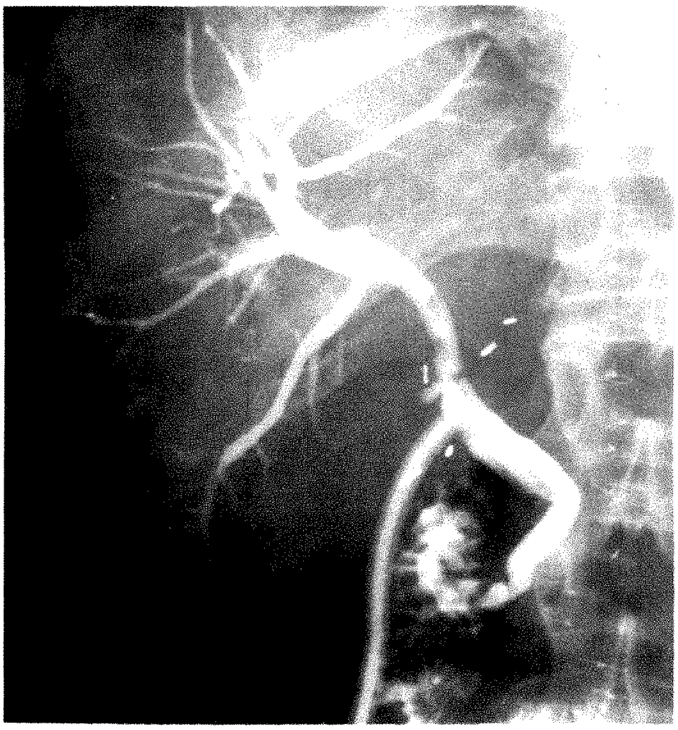


FIG. 16. Dye injection demonstrating T-tube passing through an obstructing carcinoma providing adequate bile drainage via the right hepatic duct system. Left hepatic duct completely obstructed.

Hepatic duct carcinoma

These four cases demonstrate certain results that may be expected and certain principles believed to be important when lobar and segmental ducts are drained in treatment of carcinoma of the biliary tract. In the first case (L.D.), normal liver function was restored with drainage of both the right and left ducts after a small T-tube into the right system and restricted drainage of the left hepatic ducts had been only partially effective. Case 2 (C.F.) regained normal serum bilirubin and alkaline phosphatase levels with drainage of the left hepatic duct only. Case 3 (H.C.) responded in a similar fashion with drainage limited to the right ductal system. And, finally, in the fourth case (E.Z.), a partial drainage of the ventral-cranial segment of the right lobe has resulted in symptomatic improvement but has not provided sufficient biliary drainage to lower the bilirubin or to bring the alkaline phosphatase to normal.

Conclusion

The various conditions discussed above, when they involve the segmental or lobar hepatic ducts, have a remarkably limited number of effects on the biliary system. Basically, they produce one of four responses singly or in combination: 1) Obstruction to the flow of bile; 2) precipitation of particulate matter and formation of

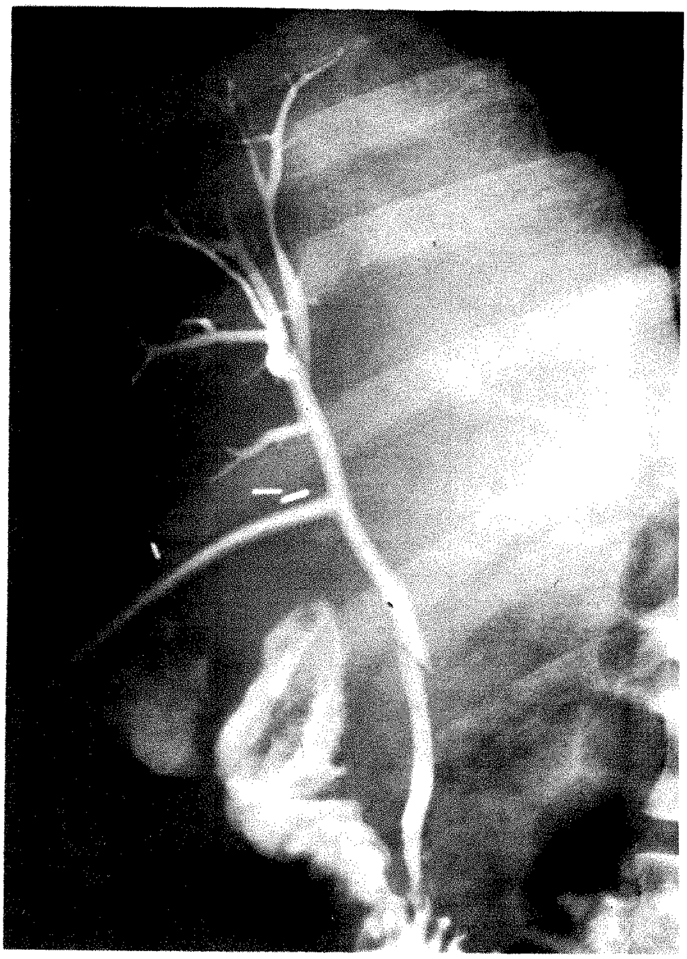


FIG. 17. T-tube cholangiogram indicating partial drainage of ventral-cranial segment of right lobe. Moderate elevation of serum bilirubin persists. Otherwise the patient is asymptomatic.

stones; 3) development of infection; or 4) creation of an external biliary fistula.

Obstruction and infection have important secondary effects on the liver parenchyma: complete biliary obstruction, resulting in hepatic atrophy; and partial obstruction, particularly when associated with infection, causing hepatocyte destruction, periportal scarring, and ductal sclerosis.

In certain rare cases, if the infection escapes beyond the liver via the lymphatic or hepatic veins, the systemic effects of infection, i.e., gram-negative sepsis, become a part of the clinical picture. Partial obstruction, although it may, at times, be produced by stones, will of itself ultimately lead to the formation of stones and the development of infection.

Bland obstruction of the biliary system without infection is remarkably well tolerated. Despite previous reports to the contrary, evidence seems clear that unobstructed biliary drainage of 50% of the liver parenchyma through either the right or left hepatic ducts is adequate to restore normal liver function, even if the obstructed lobe remains in situ. It is probably necessary, however, that the hepatocellular function of the drained lobe be normal and the ductal system uninfected. The presence of undrained liver tissue is probably of no significance as long as it is completely obstructed and uninfected. A partially obstructed lobe or segment, particularly when associated with infection, will, on the other hand, lead to hyperbilirubinemia with the clinical signs of jaundice, pruritis, and sepsis. The exact mechanism whereby partial obstruction produces such symptoms is not understood.

These concepts have important connotations in the management of segmental or lobar duct lesions, for unless there is a good chance that an unobstructed, uninfected biliary flow can be achieved through such a duct, it is better that it be completely obstructed and its drainage area allowed to atrophy.

An intrahepatic abscess, in communication with an obstructed or abnormal biliary tract, will generally require resection of the involved liver and repair of the abnormal bile duct should the lesion of the bile duct be situated in a portion of the biliary system that drains both normal and abnormal portions of the liver.

Symptoms resulting from diffuse intrahepatic duct abnormalities may be ameliorated, at least in part, by a large extra-hepatic duct-enteric anastomosis.

Intrahepatic stones are seen in: 1) patients who have had multiple common duct stones for long periods of time with secondary dilatation of the ductal system or 2) those with congenital anomalies of the ductal system (usually saccular or diffuse dilatation) and secondary stone formation.

After removal of intrahepatic stones using all available techniques, including endoscopy, a choledochoenterostomy should be performed if there is a question of retained or recurrent stones or if the ductal dilatation is the primary condition and stone formation secondary. Intrahepatic stones are usually asymptomatic until they pass down into the main biliary channel to produce biliary obstruction and cholangitis. Passage of the stone through the choledochoenterostomy will, of course, prevent this sequence of events. Impacted intrahepatic stones with distal infection may require hepatic resection.

Unimpeded drainage of either the right or the left hepatic ductal system via a large T-tube through the point of obstruction or by duct-enteric anastomosis above the obstruction can provide satisfactory palliation of malignant biliary obstruction due to carcinoma of the bile duct when the tumor cannot be excised.

Finally, it should be emphasized once again that frequent anomalies of the extrahepatic ducts play an important role in provoking injury of the biliary apparatus during cholecystectomy. Knowledge of the common anomalies, their recognition and management, is essential for the surgeon.

Addendum

Since completion of this manuscript, we have treated another patient with an unrecognized right dorsal caudal segmental duct injury sustained during cholecystectomy. Recovery was complicated due to inadequate drainage of intraperitoneal bile, but the biliary fistula eventually closed spontaneously. Postoperative x-ray films obtained by the injection of radiopaque solution through the biliary fistula suggested that the divided duct opened into the bed of the gallbladder.

J.S., a 37-year-old man, underwent cholecystectomy for cholelithiasis on August 20, 1974. Three weeks after an uncomplicated operation and an initial uneventful postoperative course, the right upper quadrant was reexplored because of pain. A massive subhepatic and subphrenic accumulation of bile was drained. Bile seemed to be coming out of the bed of the gallbladder. Thereafter, approximately 400 cc of bile was drained per day, but he continued to have normal-colored stools. On October 18, 1974, the following test results were obtained: Prothrombin time 100%, serum creatinine 1.1 mg/100 ml, total protein 9.2 gm/100 ml, albumin 4.65 gm/100 ml, cholesterol 151 mg/100 ml, glucose 103 mg/100 ml, total bilirubin 0.7 mg/100 ml, alkaline phosphatase 265 units, SGPT 150 units, SGOT 89 units, white blood cell count 8,300/cu mm, hematocrit 38.8%, hemoglobin 12.6 gm/100 ml. X-ray findings were as follows: A sinogram demonstrated a "pocket" of dye in the region of the gallbaldder fossa; the dye then filled a part of the intrahepatic ductal system in the region of the right dorsal caudal segment. No dye was seen to enter the extrahepatic biliary tract. Cleocin was given for 4 days following one episode of temperature elevation to 100.6 F on October 12, 1974. This febrile episode was associated with reduced biliary drainage from the fistula. At the time of the patient's admission to the UCLA Hospital on October 30, 1974, slight tenderness was present over the right costal margin. Biliary drainage had stopped. His temperature was 99 F, white blood cell 9,100/cu mm, total serum bilirubin 0.6 mg/100 ml, SGOT 183 units, and alkaline phosphatase 296 units. Stool and urine were normal in color. Attempted injection of the sinus tract did not disclose any communication with the biliary tree. Continued observation was recommended, and in the ensuing months, the patient has remained well without biliary drainage, chills, fever, or jaundice.

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DISCUSSION

DR. FRANK G. MOODY (Salt Lake City, Utah): Drs. Longmire and Tompkins have presented with clarity approaches to problems which occur at or above the bifurcation of bile ducts. The principles they have enumerated are not far different from the ones we use for problems in the lower biliary tree, that is removal of debris and the establishment of free egress of bile especially when it's infected.

When you read the manuscript as I have, you'll try to second guess them on the cases that they present, but I assure you that you won't improve on their results; I imagine you guessed that when you heard the presentation.

There are many personal preferences in managing problems of this type. For example, in patients who have congenital or adult cystic lesions that are stone formers, I think one should leave a large T-tube into the lower bile duct so he can retrieve, at intervals, stones which are often formed in these patients. Evacuation of the biliary tree in these patients is just not enough and I personally don't believe that the provision of a choledochoduodenostomy is going to handle this problem adequately.

In regard to strictures which occur in the hepatic duct that go into the bifurcation, and I must say this is the most common lesion I seem to encounter in my practice, I think the simplest way is to make an incision through the stricture from the hepatic duct up into the primary radicals and then place a Roux limb over this area.

As regards malignant lesions in this area, occasionally you can resect them. I believe they do report on two such cases. I had one such case. In this instance, the question is whether you should put both limbs of the biliary tree back in your Roux limb. Dr. Longmire and Dr. Tompkins have made very important contributions here because they tell us that you don't have to do this and I certainly agree with them. In terms of the majority of these lesions, however, you're lucky if you can establish drainage with the Roux limb. I prefer to do this by bringing it up to the left duct. If you divide the left branch of the portal vein, it gives you access to the radical large segment of the left ductal system that is in this area.

Now, I take issue with just one point because I don't know how to establish this and that is whether, in fact, you are dealing with an infected biliary tree, especially in these strictures that occur at the bifurcation because many of these patients have been on suppressive doses of antibiotics. At the time that you see them, they don't show frank signs of cholangitis. I would like to ask Dr. Tompkins to tell us how he establishes, either prior to or at the time of surgery, whether he's dealing with an infected biliary tree. Secondly, will just tying off the duct and allowing the lobe to atrophy lead to biliary cirrhosis?

Finally, do they have long enough followup on their patients to assure us that indeed it is not necessary to re-establish drainage in these ducts.

DR. THOMAS E. STARZL (Denver, Colorado): I would like to discuss just one aspect of Dr. Longmire's paper, namely the treatment of the small intrahepatic duct cell carcinomas that can obstruct the confluence of the right and left hepatic ducts.

(Slide) This is an example of such a lesion in a 48-year-old man as seen by a transhepatic cholangiogram. His liver was removed and replaced with an orthotopic homograft 15 months ago. This is the specimen and this is an intravenous cholangiogram of the new duct system in which the duct reconstruction was with a cholecystojejunostomy to a Roux limb. We have treated three such patients with liver replacement. (Slide) The recipient I just described and this second 43-year-old patient, who is now nine months after operation for this lesion, have normal liver function and no evidence of recurrence. The third patients, who was 63 years old, died early postoperatively because of a technical error which I made during the transplant procedure.

It has begun to seem to us that small intrahepatic duct carcinomas may be a reasonable indication to perform total liver replacement in relatively young recipients. In contrast to the situation with large and nonresectable hepatomas, recurrence of the tumor has not occurred, at least so far. As Dr. Longmire showed us at the 1973 American Surgical Association meeting, autotransplantation of the lateral segment may be an attractive alternative approach in favorable cases. And in a few others, partial hepatectomy may be possible, as Dr. Longmire described in two cases today. In any event, trying for a cure instead of palliation in some of these patients is an appealing prospect that deserves further exploration.

DR. JOHN WILLIAM BRAASCH (Boston): It gives me a great pleasure to discuss this paper of Drs. Longmire and Tompkins, first of all because it is the most comprehensive treatment of the subject of segmental and lobar surgical disease of the liver available, and secondly, because this subject has been kind of a hobby of mine for quite awhile.

Not only is the etiology of the jaundice which occurs with fractional biliary outflow occlusion of interest but also, as the authors have emphasized, the practical application of these observations is very important.

To underline this importance is the case of a double traumatic stricture which required a double hepaticojejunostomy three years ago. The right anastomosis which I performed was two inches within the liver substance at that time and when she returned last week with cholangitis, I was determined to resect her right lobe since it didn't seem possible to establish a satisfactory right hepaticojejunostomy again. Unfortunately, this proved not to be feasible since the blood supply to the left lobe came mostly from the right hepatic artery on angiography. So, at surgery after dilating the left hepaticojejunostomy and being unable to locate the right duct, we left the right lobe in place having just read Drs. Longmire and Tompkins' manuscript the night before. Hopefully, this right lobe will quietly fade away as they have suggested.

Unfortunately, our previously published experience with 11 cases of only left hepaticojejunostomy in the course of stricture repair has not given too much support to this hope since in only three was the result satisfactory.

Now, in this present report, there are six cases which have a bearing on the problem of fractional obstruction jaundice. In three, the proof of obstruction was radiologic, on T-tube cholangiograms, and the patients were not jaundiced. In one, the proof was also radiologic and there was jaundice. That leaves two cases in which the proof of obstruction was surgical and each of these patients was not jaundiced. One had an obstructed right hepatic duct and another an obstructed posterior segmental duct.

There are many uncertainties in trying to evaluate these cases. Is a T-tube cholangiogram which fails to fill part of the biliary tree valid evidence for obstruction? Most often it is, but not always. Does a temperature elevation on one occasion mean that bile in an obstructed duct is infected? Is there an anomaly present such as is shown in this slide in which the posterior segmental duct crosses over and joins the left duct high up inside the liver? In this situation, part of the right lobe is drained by the left duct.

All of these unanswerable questions cloud valid assumptions but in spite of these problems, I would agree with the authors that probably development of jaundice in fractional obstruction depends on the presence or absence of infection and the amount of liver obstructed. My own preference is to emphasize the latter, but certainly the former is very important as they have shown. We only need to recall that appreciable degrees of jaundice can follow acute cholecystitis without physical common duct obstruction.

I have two other points to make. Both concern the treatment of segmental sepsis. (Slide) This is a barium cholangiogram of a patient who had a stricture repair previously. He had been having frequent chills and fever for several months and you will note that the anterior segmental ducts did not fill. Rather than risk a right hepatectomy in this elderly, politically sensitive case, a dilator was forced through the occluded duct to drain an abscess with subsequent relief of symptoms. This then is an alternative procedure to hepatectomy for segmental sepsis.

My second point concerns the management of segmental sepsis which occurs without known benign ductal obstruction. One must be sure that a neoplasm which should be included in the resection has not obstructed the duct draining the area of sepsis.

PROFESSOR MAURICE PAUL MERCADIER (Paris, France): As I have a very bad Quebec accent, I will try to speak in English in the same way! About the lesion of right or left hepatic duct, as with Dr. Longmire I usually put a ligature on the duct.

I am not sure it is possible to get it across when you have such a stricture at the region of the common duct. You have biliary cirrhosis on dilatations of the duct and I think it's quite exactly the same.

About the lesion with infection at the liver at the confluence of a duct, I don't like to perform an hepatectomy of the left hepatic turn.

I think it's always possible to reach the confluence. You can do that below the liver at the level of the islets affecting the capsular. It is always possible, at least in my practice, to perform anastomosis, a large anastomosis with the left branch.

If you can reach the bile ducts from below, it's always possible to reach the confluence from the top from above.

You can perform two operations. They were described by Chaumpeau in France and I have practiced some of them. You can do a midline incision at the level of the liver on the right side. Through the parenchyma you can reach the hylus on the confluence of the two ducts and perform an anastomosis, a large anastomosis, with the right hepatic duct especially with long hepatic duct.

Sometimes it's not necessary to do such an operation. You can remove the interior aspect of the fourth segment of the liver between the medium then on the ligament and you can reach exactly the confluence of the two hepatic ducts, the main hepatic ducts.

We have performed such operation very rarely, but quite often it's impossible to repair such a lesion with the left hepatic duct from below.

As the Chiari Disease, I think I was the first to perform a hepatic for Chiari Disease. I agree with you when you have dilatation on the right part of the liver, on the left part of the liver it's always possible to perform an hepatorrhaphy and I have performed a large right hepatorrhaphy in my first case.

But when you have dilatation on both sides, I have performed in a similar case, a second case of Chiari's Disease, I have performed exactly the same operation I described for a stricture, a midline incision on the left side of the median vein, the liver is opened just like a book and it's not bleeding not at all with a finger fracture of the parenchyma. It's very easy to control the collaterals of the median vein and you reach the confluence of the right bile duct by the left bile duct and you can perform a very large anastomosis with a Rouen-Y loop of jejunum.

I think it is very important always to have the long loop to avoid the reflux. To me that means 60 cm at least.

As for stenosis from a carcinoma, I think it is quite an operation to perform a liver transplant. In many cases, you see the patient when he is in very poor condition and I think it's quite an operation to perform a liver transplant for such disease. At least this is my experience.

Dr. Ronald K. Tompkins (Closing discussion): Dr. Moody, we agree that the T-tube may be left in for irrigation of these multiple cystic areas. We would like to be able to get to them early enough so that we do not have such a large amount of sludge that it can't be removed and in those cases feel that a high duct-enteric anastomosis may prevent the stagnation and sludging.

We do have, at present, some patients with tubes in who need the irrigations for relief of sludge periodically.

You ask a very difficult question and that is how do we know if the biliary tract is infected? Most of us have seen patients with bacteria growing in the bile ducts and around the tubes quite frequently and yet the patients get along quite well. I would guess that the best answer is if the patient has signs and symptoms of cholangitis then we would say that this is a significant infection.

There is a difference, clinically, I think between a bacterobilia and an infected biliary tract and this is a very difficult clinical judgment in some cases.

The other difficult question you asked was whether tying off the duct causes biliary cirrhosis? We can't answer that on a controlled patient series basis, however we have one patient who is now about eight years following such an operation with normal liver function and no evidence of biliary cirrhosis.

Dr. Starzl, we're very interested in your three transplantations for bile duct carcinoma. I think that with the present dismal results of the treatment of bile duct carcinoma that such innovative attempts at therapy and cure are indicated and especially in experienced hands such as yours.

However, I would point out that the course of patients with bile duct carcinoma in many cases is a prolonged one and that 15 months followup is rather short for some of these. We look forward to further followup on your cases in the future.

Dr. Braasch, of course, is well known for his detailed studies in the area of segmental obstruction and damage to the liver. We appreciate his comments and have benefited by his experiments and experience.

We agree with him that the etiology of the jaundice in some of these patients is a mystery and I certainly hope that his latest patient continues to do well.

We feel that a T-tube cholangiogram done in the x-ray department is adequate because we can make use of gravity, turning the patient to various sides and fill the ductal segments.

The T-tube cholangiogram done on the operating table is not that accurate. We've had difficulties filling all the segments with both T-tube and cystic duct cholangiography in the operating room. This is not a problem in those institutions where movable tables and fluoroscopic equipment are available.

Dr. Braasch also asked if fever means cholangitis. I think we would answer that somewhat similarly to Dr. Moody's question.

We're quite happy in some of these difficult cases if the patient has only one, or perhaps two, episodes of fever in a year and this is manageable by antibiotics. We would agree that that is probably cholangitis but it does not necessarily warrant reoperation.

Professor Mercadier, we thank you very much for sharing with us your experience with the transhepatic exposition of the bile ducts. We have not used that procedure although we agree with you that a long Roux-Y limb is of value no matter how you drain the biliary tree. I think that your statement that it's almost always possible to perform an anastomosis to the left duct is quite right. We've found in other studies that the left hepatic duct is a long and unbranching segment beneath the liver for 3 or 4 cm in most specimens that we've looked at.

And, if one can gain access to that area through the scar and the other vascular adhesions, then I think an anastomosis is quite reasonable and in some of our cases we've shown that that's all that needs to be done, the right duct does not need to be hooked up if there's no infection behind that.

Cholecystokinin Metabolism in Man and Dogs

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We have developed a sensitive, specific and reproducible radioimmunoassay for cholecystokinin (CCK) with which basal levels of CCK of between 400-800 pg/ml have been measured in normal man, in patients with diabetes and with duodenal ulcer disease, and in normal dogs. After a meal, circulating levels of CCK rose to 1000-1200 pg/ml in human subjects. Release of CCK was more rapid in diabetic and duodenal ulcer patients than in normal subjects, but elevated postprandial levels persisted much longer in normal subjects. Patients with the Zollinger-Ellison syndrome had elevated values of cholecystokinin which rose after a meal. Lack of correlation between elevated basal levels of gastrin and CCK in patients with the Zollinger-Ellison syndrome suggest that the hypercholecystokininemia may be absolute. The disappearance half-time of exogenous CCK was about 2½ minutes in normal subjects as well as in diabetic and duodenal ulcer patients. Studies in dogs demonstrated no uptake of basal levels of cholecystokinin by the kidney; on infusion of exogenous CCK-33, the kidney extracted 43% of the total CCK presented and 56% of the integrated CCK. We conclude that: 1) circulating basal and postprandial levels of CCK may be measured in a reproducible fashion; 2) postprandial release of CCK is more rapid in diabetic and duodenal ulcer patients than in normal man; 3) the disappearance half-time of exogenous CCK in man and dogs is about 2½ minutes; 4) the kidney is a major site for uptake of CCK.

IN 1856 Claude Bernard reported that introduction of hydrochloric acid into the duodenum resulted in stimulation of bile flow.[1] Ivy and Oldberg[19] demonstrated in 1928 that extracts of small intestinal mucosa caused contraction of the gallbladder; they called the active material cholecystokinin. In 1943 Harper and Raper[15] extracted a potent stimulant of secretion of pancreatic enzymes from small bowel mucosa and they named the agent pancreozymin. The meticulous studies of Mutt and Jorpes[20,21] have culminated in the isolation and chemical characterization of a single polypeptide which possesses the biologic activities ascribed to both hormones. Because cholecystokinin was discovered first, it is now conventional to refer to the polypeptide hormone as cholecystokinin with the knowledge that it has multiple actions besides stimulating gallbladder contraction (stimulation of pancreatic enzyme secretion and stimulation of gastrointestinal smooth muscle,[3] *inter alia*[33]).

Precise studies on the metabolism of cholecystokinin (CCK) have been hindered by lack of precise methods for measuring physiologic concentrations of the hormone. Cholecystokinin is structurally similar to gastrin (the C-terminal 5-amino acid residues are identical), and the two hormones share several actions.[33] In addition, secretin may be released from small bowel mucosa at the same time as CCK and their actions overlap.[22]

Two years ago we reported development of a radioimmunoassay which allowed measurement of the endogenous release of cholecystokinin.[29] Difficulties with early radioimmunoassay methods for CCK have been recently reviewed;[9] our current method is reliable, sensitive and reproducible.[25] In the present study we report precise measurements of release of CCK in normal persons, in diabetic and duodenal ulcer patients and in patients with the Zollinger-Ellison syndrome. The disappearance half-

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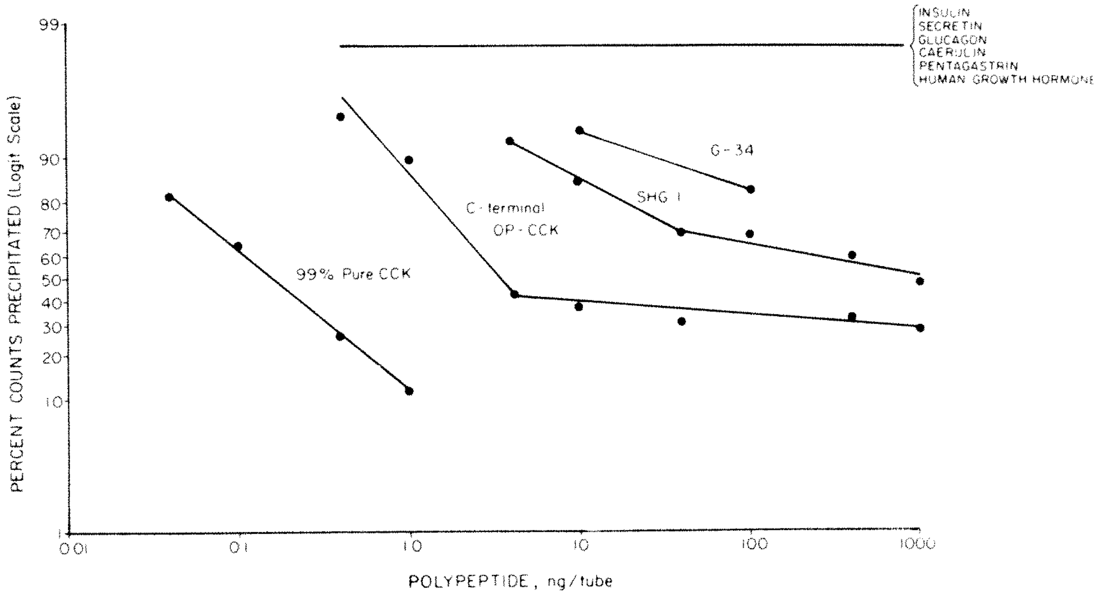

FIG. 1. Dose-response curves of graded amounts of 99% pure CCK and other polypeptide hormones in the CCK radioimmunoassay, with 99% pure CCK used as a labeled antigen.

time for CCK in man is calculated, and studies in dogs are reported which show that the kidney plays an important role in the catabolism of CCK.

Materials and Methods

Radioimmunoassay

The current radioimmunoassay technique[25] differs from our previously reported assay,[26,28,29] in that 99% pure CCK (3000 IDU/mg) (obtained from the Gastrointestinal Hormone Laboratory of the Karolinska Institute, Stockholm) is now used both as the labeled antigen and as the reference standard. The assay technique has been described in detail;[25] a summary of the method will be provided for clarity.

Antiserum was generated in New Zealand white rabbits by the method of Vaitukaitis and colleagues[38] in which 16% pure CCK (500 IDU/mg) (also obtained from the GIH Laboratory, Karolinska Institute) was used as an immunogen. Booster injections of the immunogen were given biweekly and the rabbits were bled on alternate weeks. The antiserum selected (UT122) bound 25%-35% of labeled antigen at a final dilution of 1:2500. Labeled 99% pure cholecystokinin was iodinated with carrier-free ^{125}I to specific activities of 30-50 μci/μg by the method of Greenwood, Hunter and Glover.[13]

For each CCK radioimmunoassay, 99% pure CCK was used as a reference standard and dose-response curves were generated by the method of Rodbard.[31] CCK concentrations were calculated as picograms per milliliter (pg/ml).

To test the specificity of the assay, we measured the ability of other polypeptide hormones (some whose molecular structure resembles that of CCK) to displace labeled CCK from combination with antiserum. A standard dose-response curve was generated with varying doses of 99% pure CCK, and was compared with that of other hormones (Fig. 1). Insulin, secretin, glucagon, caerulein, pentagastrin, and human growth hormone did not compete with labeled cholecystokinin for antibody sites in quantities ranging from 4 to 1000 ng per tube. The C-terminal octapeptide of CCK (Op-CCK, gift from Dr. Miguel Ondetti, Squibb Laboratory), synthetic 17-amino acid human gastrin I (SHG I) and natural 34-amino acid human big gastrin (G-34, gift from Professor R. A. Gregory) did effect displacement of labeled CCK from CCK antibody, but the lines of inhibition generated were not parallel to the dose-response curve of 99% pure CCK. Compared to the mass of 99% pure CCK required for an equivalent displacement of labeled cholecystokinin from combination with antibody, the mass of Op-CCK was 25 times greater, the mass of SHG I was 400-500 times greater, and the mass of G-34 was 1000-1250 times greater. Since there is only slight cross-reaction with Op-CCK, which contains the biologically active segment of the molecule, it would appear that this antibody (as well as all other CCK antibodies yet reported[9]) recognizes chiefly the nonbiologically active segment of the molecule.

The reproducibility of the assay was tested in a study in which 5 replicate measurements of CCK in human serum were made in 4 separate radioimmunoassays. The intra-assay coefficient of variation was 4.5% and the between-assay coefficient of variation was 12.5%.

In order to test the ability of the assay system to quantify CCK in serum, graded volumes (50-500 μl) of serum taken from a patient with the Zollinger-Ellison syndrome, were analyzed in the radioimmunoassay. This patient previously had been shown to have high levels of

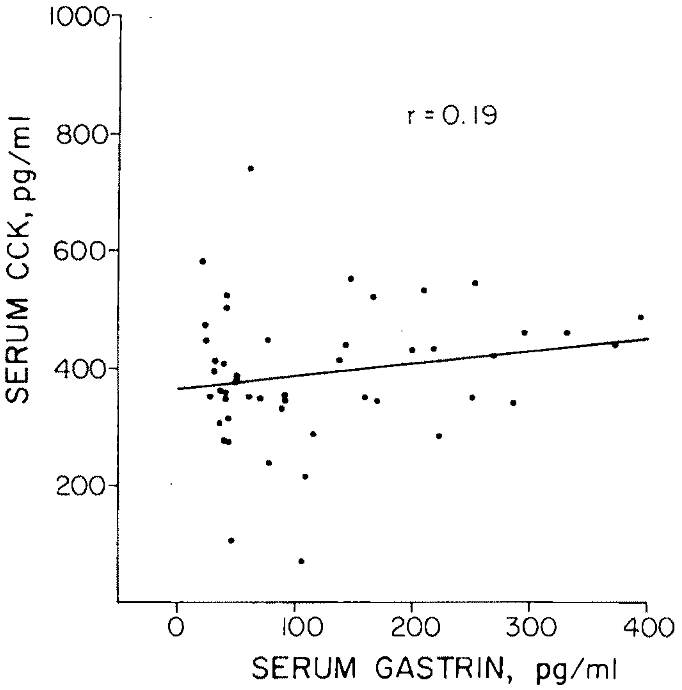

FIG. 2. Plot of simultaneously measured concentrations of CCK and gastrin from four individual patients in the fasting and in the postprandial state. Concentrations of gastrin were used as the independent variable and concentrations of CCK as the dependent variable.

CCK in serum. The dose-response curve of the endogenous CCK in serum and the dose-response curve generated by 99% pure CCK, were exactly parallel, which indicated that the assay system can accurately quantify CCK in serum.[25]

To test the ability of the assay to distinguish between endogenous gastrin and CCK in serum, we obtained 48 serum samples (from four individuals) collected before and at intervals after a meal to provide comparison of simultaneous gastrin and CCK concentrations. Serum concentrations (expressed as pg/ml) were measured with a specific radioimmunoassay for gastrin[24] and for CCK.[25]

The mean basal concentration of serum gastrin was 95±18 pg/ml; this increased to a peak postprandial level of 167±77 pg/ml. Mean basal CCK concentration was 413±66 pg/ml. This level rose to a postprandial peak of 526±42 pg/ml. Comparison of the gastrin and CCK concentrations by unweighted linear regression analysis, resulted in the calculation of a correlation coefficient (r) of 0.19 (Fig. 2). This weak correlation indicates that serum CCK levels measured in the radioimmunoassay system were not influenced by changes in serum gastrin values.

Concentrations of CCK in Man

Studies were performed on 69 subjects; informed consent was obtained from each person.

Release of CCK by food. The effect of the administration of a liquid test meal (250 g Sustagen) containing 166 g carbohydrate, 59 g protein, and 9 g fat on the circulating level of CCK, was studied in 16 normal subjects, 13 insulin-dependent diabetic patients, 12 patients with proven duodenal ulcer (preoperative), 8 proven duodenal ulcer patients studied 2-16 weeks after selective proximal vagotomy, and 11 patients with histologically proven Zollinger-Ellison syndrome, studied at various periods after total gastrectomy. They were fasted for at least 14 hours prior to the study and blood samples were collected twice before the meal and at regular intervals after eating.

Disappearance half-time (T½) of exogenous CCK. The rate of disappearance of exogenously administered CCK was studied in 4 normal subjects, 4 insulin-dependent diabetics, and 4 patients with proven duodenal ulcer before operation. Blood samples were collected from fasting patients immediately before the intravenous 5-minute infusion of either 0.5 or 1.0 IDU/kg/min of 16% pure CCK. Further samples were obtained at 3 minutes after the initiation of the infusion, at the end of the 5-minute infusion, and after the infusion at 1-minute intervals for 10 minutes and then at 2-minute intervals for an additional 10 minutes. Serum samples were collected and stored frozen until assayed for CCK. The disappearance half-time of exogenous cholecystokinin was calculated by linear regression analysis.[39] The mean basal concentration of cholecystokinin was subtracted from all subsequent values for each person in the study. The peak concentration of CCK at the end of the infusion was assigned a value of 100% and the value for each subsequent time period was calculated by dividing each CCK concentration by the peak value. Per cent values were then converted to natural logarithms and the data were analyzed by linear regression analysis with time used as the independent variable and the natural logarithm of the per cent of the peak CCK concentration as the dependent variable. This analysis resulted in an equation of the regression line:

$$y = a + bx$$

where: $y = \log_e$ per cent peak CCK concentration;
a = value of y when $x = 0$;
b = slope of the regression line;
and x = time in minutes.

The disappearance half-time was then calculated by dividing 0.693, the natural logarithm of 2, by the slope of the regression line.

Renal Uptake of CCK in Dogs

Four mongrel dogs weighing between 18-25 kg were anesthetized with pentobarbital sodium after an overnight fast. The right brachial vein was cannulated and a catheter was passed into the aorta via the left femoral artery. A midline laparotomy incision was performed and the left renal vein was cannulated by way of the left femoral vein. Basal blood samples were obtained from the aorta and the renal vein after which an infusion of

16% pure CCK (1 IDU/kg/min) was administered for 5 minutes to each dog. Samples were obtained from the aorta and renal vein at the end of the 5-minute infusion and at 1-minute intervals for the next 5 minutes.

Statistical Note

Results are expressed as the mean ± one standard error. The Student 't' test was used to analyze the data for statistical significance of differences between means. Differences with a P value of less than 0.05 were considered significant.

Results

Concentrations of CCK in Man

Release of CCK by food. The mean basal concentration of CCK in 16 normal subjects was 728±84 pg/ml. This level rose to a peak at 60 minutes after food to 1079±101 pg/ml and 4 hours later was still elevated (1146±143 pg/ml). Samples obtained at 30, 60, 90, 180, and 240 minutes after food were elevated significantly above basal (Fig. 3).

In 13 insulin-dependent diabetic patients, the mean basal concentration of CCK was 542±94 pg/ml, which rose briskly after a meal to a peak of 797±112 pg/ml at 15 minutes. Only the 5-minute and the 15-minute samples were elevated significantly above basal. At 90 minutes, the value was 604±78 pg/ml and at 180 minutes the concentration was 636±118 pg/ml (Fig. 4).

The mean basal concentration of CCK in 12 preoperative patients with duodenal ulcer was 630±71 pg/ml, which rose rapidly to a peak of 1003±194 pg/ml at 15 minutes. Postprandial concentrations of CCK in preoperative patients were elevated significantly above basal levels at 5, 15 and 30 minutes. At 180 minutes after food, serum CCK was 741±77 pg/ml (Fig. 5). In 8 duodenal ulcer patients after selective proximal vagotomy, the mean basal concentration of CCK was 709±95 pg/ml, which rose to 1305±299 pg/ml at 30 minutes. Only the 15-minute and 30-minute postprandial samples were elevated significantly above normal, and the concentration of CCK at 180 minutes after eating was 614±59 pg/ml (Fig. 5). The observed differences between values in preoperative and in postoperative duodenal ulcer patients were not significant.

The mean basal concentration of CCK in serum of 11 patients with the Zollinger-Ellison syndrome (after total gastrectomy) was 1628±320 pg/ml. Because of wide variations among patients, this concentration was assigned a value of 100% and postprandial levels were compared to it. The peak postprandial concentration of 140±18% was achieved at 15 minutes; samples at 15, 60 and 90 minutes after food were elevated significantly above basal. By 150 minutes, CCK concentrations had returned to basal (Fig. 6).

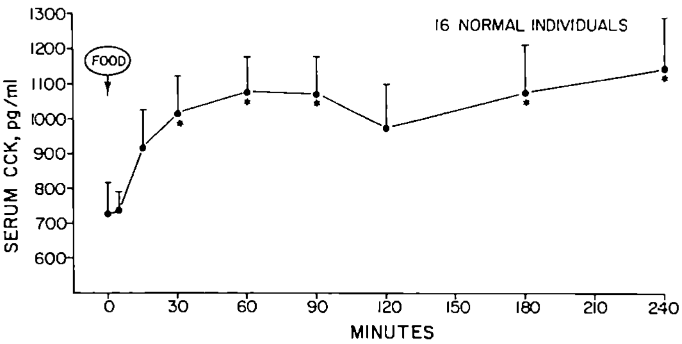

FIG. 3. Concentrations of serum CCK (pg/ml ± SE) in 16 normal subjects before and at different time periods after the ingestion of a high-protein, high-carbohydrate liquid meal. Asterisks identify values which are elevated significantly above basal.

Disappearance half-time of exogenous CCK. Exogenous CCK was removed rapidly from circulation and was virtually undetectable at 14-15 minutes after the infusion was stopped. The calculated disappearance half-time was 2.4 minutes in normal subjects, 2.7 minutes in diabetic patients and 2.4 minutes in duodenal ulcer patients (Fig. 7). All correlation coefficients (r) were significant.

Renal Uptake of CCK in Dogs

The mean basal concentration of cholecystokinin in serum obtained from the aorta in 4 dogs was 441±63 pg/ml; basal serum from the renal vein had a mean concentration of CCK of 463±76 pg/ml. At the end of the 5-minute infusion, the concentration in the aorta was 3053±417 pg/ml and the simultaneous concentration in the renal vein was 1729±368 pg/ml (Fig. 8). All postinfusion concentrations in the renal vein were lower than in the aorta. Differences at 5 and 7 minutes were significant.

In order to demonstrate the cumulative differences between concentrations of CCK in the aorta and in the renal vein during the 10-minute period after the infusion was

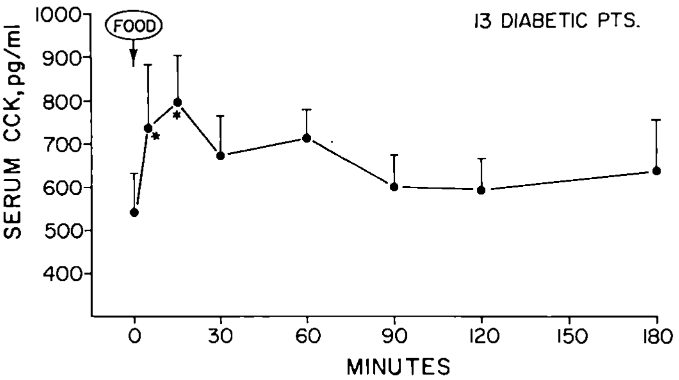

FIG. 4. Concentrations of CCK (pg/ml ± SE) in the serum of 13 insulin-dependent diabetic patients before and at different time periods after the ingestion of a high-protein, high-carbohydrate liquid meal. Asterisks identify values which are elevated significantly above basal.

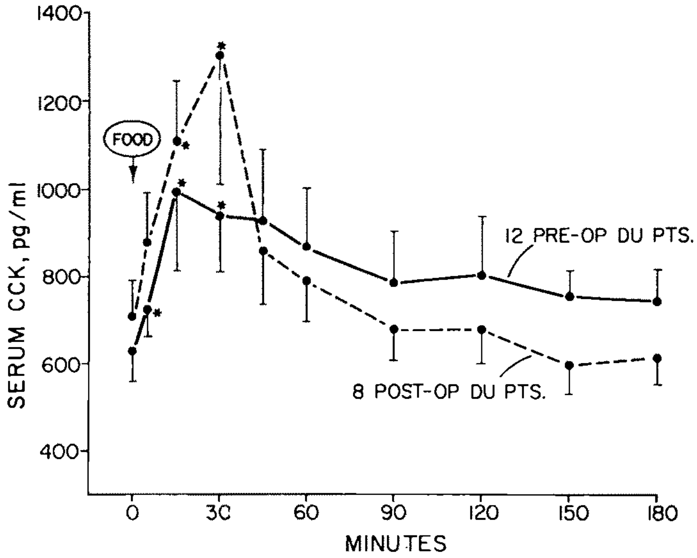

FIG. 5. Concentrations of serum CCK (pg/ml ± SE) in 12 preoperative patients with duodenal ulcer and in eight patients studied at varying time periods after selective proximal vagotomy. Samples were obtained before and at different time periods after the ingestion of a high-protein, high-carbohydrate meal. Asterisks identify values that were significantly elevated above basal. The differences in concentrations obtained from preoperative patients were not significant as compared with postoperative patients.

begun, the integrated cholecystokinin responses in the aorta and renal vein were calculated (Fig. 9).[35] The integrated response during a given period is the difference between the mean *stimulated* CCK concentration and the mean *basal* CCK concentration during the period of study. The units for expression of integrated CCK response are pg-min/ml. The integrated CCK response 0-10 minutes in the aorta was 14,626±1037 pg-min/ml and in the renal vein was 6394±1874 pg-min/ml; this difference was significant.

A linear relationship existed between the arterial serum CCK concentrations and the arteriovenous difference in serum CCK concentrations (Fig. 10). The mean regression equation was $y = -376.1 + 0.58x$ and the coefficient of correlation was 0.98 ($P<0.01$).

Discussion

Several radioimmunoassays for cholecystokinin have been described.[8,10,11,16–18,26,28,29,40] Our present assay[25] is an improvement over the method used previously.[26,28,29] The current method uses a different antibody and uses 99% pure CCK as both a labeled antigen and as a reference standard. The 99% pure CCK was found to be about 25 times more immunopotent than the 16% pure CCK used in previous assays.[25] Use of the less pure CCK preparation for dose interpolation resulted in higher estimates of concentration of CCK in test samples. Basal concentrations of CCK in normal subjects in this study were measured at about 700 pg/ml, a value that is between 1/7 and 1/25 that reported previously.[29] Harvey and colleagues have reported fasting levels in man of between 25 pg/ml[16] and 60 pg/ml.[17] This difference may be due to antibody selectivity. CCK has been reported to exist in at least two molecular forms (a 39-amino acid variation [CCK-39] and the currently available 33-amino acid molecule [CCK-33]).[6,23] The antibody used[16,17] might recognize only one molecular form (as Hansky and colleagues[14] found with a specific gastrin antibody). One CCK antibody, developed with porcine CCK as immunogen, was found not to cross-react with human CCK.[11]

Although our present antibody for CCK reacts only slightly with 17-amino acid synthetic gastrin and with natural 34-amino acid gastrin (Fig. 1), and although there seems to be little correlation between levels of serum gastrin and levels of CCK in the same patients (Fig. 2), it is still important to note that results of this assay when used for determination of serum CCK levels in patients with the Zollinger-Ellison syndrome (whose serum gastrin levels are often extremely high) should be interpreted with caution. In practice, we have found no correlation between high levels of gastrin and high levels of CCK in patients with the Zollinger-Ellison syndrome. (For example, one patient had a serum gastrin level of 26,000 pg/ml and a CCK level of 1200 pg/ml; another patient had a serum gastrin value of 4000 pg/ml and a serum CCK concentration of 1800 pg/ml). The mean basal concentration of 1628 pg/ml in the Zollinger-Ellison patients in Fig. 6, therefore, may represent absolute hypercholecystokininemia.

The administration of a high-protein, high-carbohydrate liquid meal evoked a release of CCK that was more rapid in diabetic patients and in patients with duodenal ulcer than in normal subjects, and there was a greater

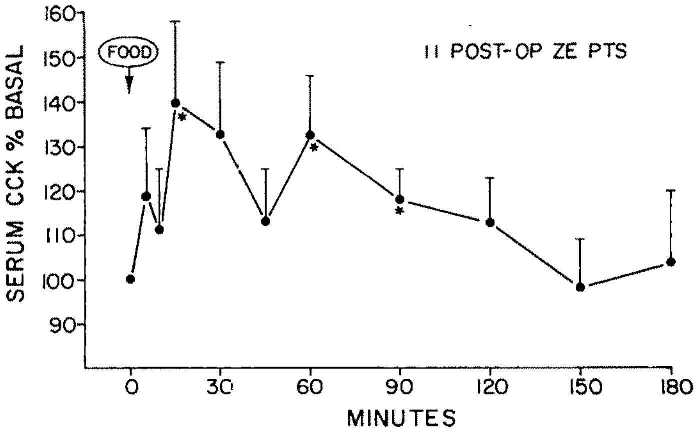

FIG. 6. Concentrations of serum CCK (pg/ml ± SE) in 11 patients with the Zollinger-Ellison syndrome studied at varying periods after total gastrectomy. Samples were obtained before and at different time periods after the ingestion of a high-protein, high-carbohydrate liquid meal. Asterisks identify values which were elevated significantly above basal.

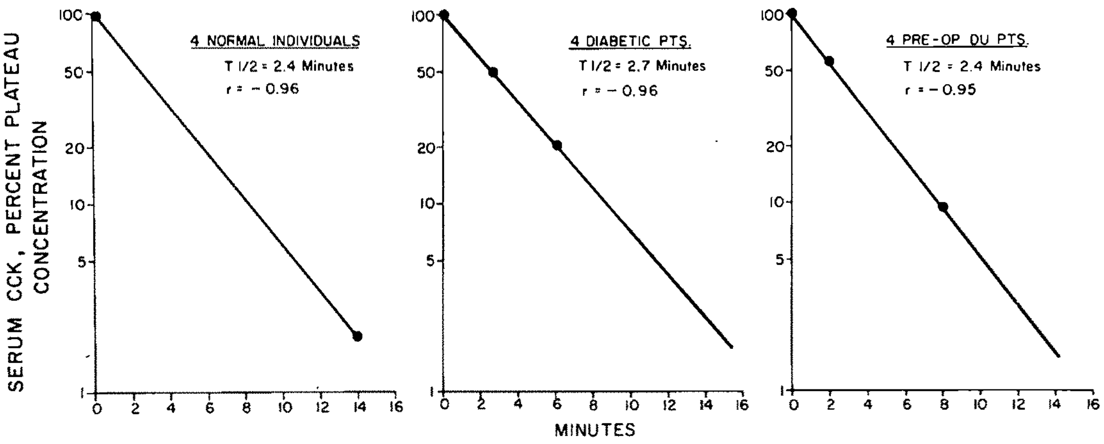

FIG. 7. Semilogarithmic plot of the disappearance half-time of exogenous CCK from circulation of four normal subjects, four insulin-dependent diabetic patients, and four preoperative patients with duodenal ulcer. Samples were obtained before, during, and at varying time periods after a 5-minute infusion of 16% pure CCK (0.5 or 1.0 IDU/kg/min). The slopes of the correlation coefficient (r) were calculated by unweighted linear regression analysis.

prolongation of elevated CCK levels in normal subjects than in diabetic or duodenal ulcer patients. Diabetic patients and ulcer patients showed significant elevation of CCK levels at 5 minutes after the liquid meal; significant elevations were not achieved in normal subjects until 30 minutes. These differences appear to be real, but their significance is not apparent. Studies on the rates of gastric emptying were not performed. An increase in the rate of emptying might be expected in ulcer patients, but not in diabetic patients.

We had previously reported[29] significant elevations of CCK at 30 minutes after a fatty meal of fried eggs, bacon, sausage, buttered toast and cream. In the present study, CCK levels in normal subjects increased steadily and significantly at 30, 60, 90, 180 and 240 minutes after food and the level was relatively constant from 30 minutes to the end of the 4-hour test period (Fig. 3). Harvey and colleagues[16] measured CCK levels in 5 healthy subjects after the ingestion of a pint of milk. They reported basal CCK levels of 25.8 pg/ml which rose to between 8 and 16 ng/ml within 35 minutes and thereafter declined rapidly, approaching basal within 45 minutes. The ratio of peak-to-basal CCK levels varied from 320:1 to 640:1,[16] as compared with the ratio of 1.5:1 in the current study. Since our subjects received a high-protein and high-carbohydrate liquid meal with higher osmolarity than the milk given by Harvey and associates,[16] the prolonged elevation of CCK in our patients may be due to retention of the hyperosmolar material in the stomach.

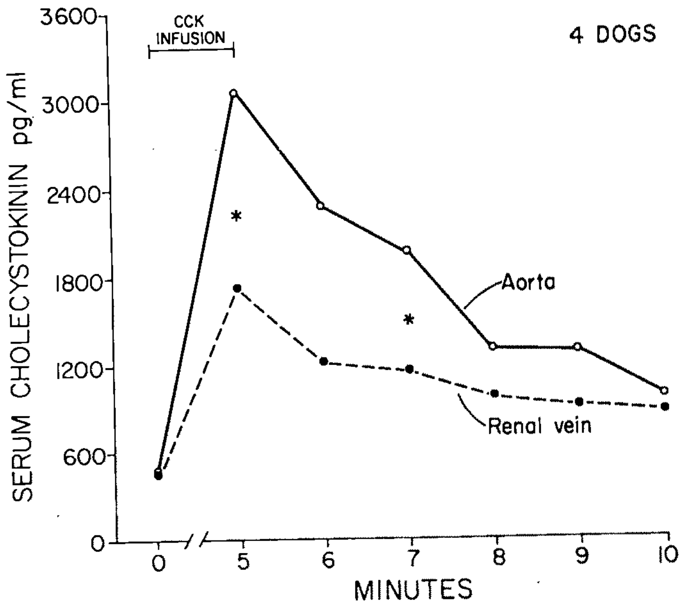

FIG. 8. Relationship between serum gastrin levels in the renal artery (aorta) and renal vein in the basal state (time 0) and after a 5-minute infusion of 16% pure CCK (1 IDU/kg/min) in 4 dogs. Asterisks denote points of significant differences.

We have previously shown that Zollinger-Ellison patients after gastrectomy have, uniformly, a brisk serum gastrin response to a meal, a response that apparently results from release of tumor gastrin by the meal.[34,37] If the high CCK values measured after food in the Zollinger-Ellison patients represent true elevations of

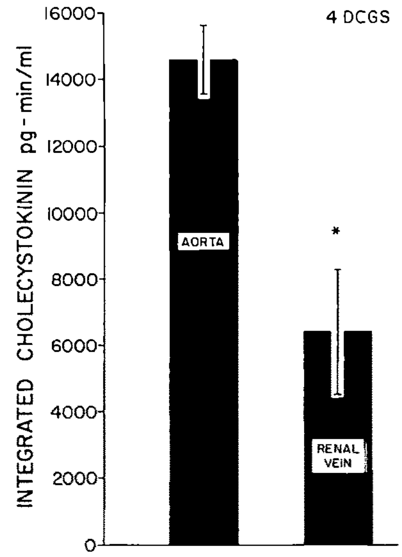

FIG. 9. Integrated cholecystokinin values, 0-10 minutes, for the study illustrated in Fig. 8. Integrated cholecystokinin value for the renal vein was significantly different than that of the renal artery (aorta).

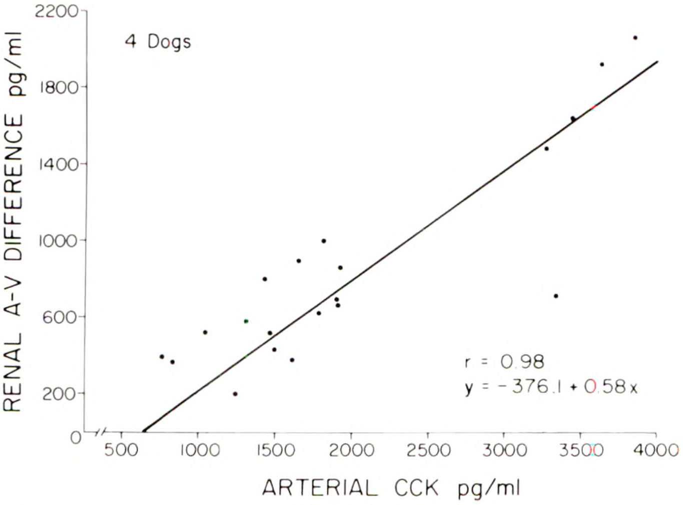

FIG. 10. Relationship of renal arteriovenous CCK difference, *y*, and arterial serum CCK concentration, *x*, in 4 dogs. r = coefficient of correlation.

CCK, the source of the large amounts of CCK might be the tumor. A CCK concentration of 0.85 μg/g of tumor has, however, been measured by us in a Zollinger-Ellison tumor that had a gastrin concentration of 587 μg/g (unpublished data). This gastrin/CCK ratio of 690:1 is within the range of cross-reactivity of the CCK assay (Fig. 1). This does not preclude the presence of significant concentrations of CCK in the tumor, nor does it support that possibility.

The disappearance half-time of exogenous CCK was remarkably similar in normal subjects and in diabetic and duodenal ulcer patients. The values agree well with the T½ we have previously reported[30] for exogenous CCK in dogs. Among the different molecular forms of gastrin, there is a direct relationship between molecular size and disappearance half-times (Table 1). Surprisingly, the T½ for exogenous 33-amino acid CCK corresponds more closely with the T½ for 17-amino acid gastrin (2.7 minutes) than it does for 34-amino acid gastrin (9 minutes[32] or 15 minutes[39]). Harvey and associates[16] suggested that the half-life of endogenous cholecystokinin in man was 5-7 minutes. We found the half-life of endogenous, that is mixed-molecular gastrin, to be 8.6 minutes in dogs.[36] Cholecystokinin has been reported to exist in at least two separate molecular forms (CCK-33 and CCK-39),[6,23] and physiologically-released CCK is likely to be a mixture of the different molecular forms.

Although levels of *endogenous* cholecystokinin, in response to food, rose more rapidly in diabetic and duodenal ulcer patients than in normal subjects and postprandial elevations persisted longer in normal subjects, the disappearance half-times of injected exogenous cholecystokinin were nearly identical in the three groups. This would suggest that if diabetic and duodenal ulcer patients do have different metabolic rates for cholecystokinin, the difference must involve mechanisms other than the catabolism of the 33-amino acid form of cholecystokinin.

TABLE 1. *Disappearance half-times (T½) of Gastrin and CCK*

Gastrins*	CCK†
Big-big gastrin—90 min.[32]	Dogs—2.6 min.[30]
Big Gastrin (G-34)—15 min.[39]	Normal man—2.4 min. (this study)
Endogenous (mixed) gastrin—8.6 min.[36]	Patients with diabetes—2.7 min. (this study)
Little gastrin (G-17)—2.1 min.[27]	Patients with DU—2.4 min. (this study)
Minigastrin (G-13)—1.8 min.[7]	

*All gastrin T½ studies were performed in dogs.
†In all CCK T½ studies, the material injected was the natural porcine 33-amino acid form of CCK.

The brief half-life of cholecystokinin in circulation suggests catabolic mechanisms that are rapid and efficient. We have previously shown that although the kidney does not take up *basal* levels of gastrin, it does extract between 30%-40% of exogenously administered G-17[4] or endogenously stimulated mixed-molecular gastrin.[2] Nephrectomy was found to cause an increase in the disappearance half-time of G-17 from 2.85 minutes to 7.88 minutes.[5] The present study indicates that the dog kidney does not extract basal levels of CCK since the concentration of endogenous CCK was the same in the renal vein as it was in the aorta. At the end of a 5-minute CCK infusion, however, 43% of the peak total CCK concentration presented was extracted by the kidney. If only stimulated levels are considered, the differences in integrated CCK (Fig. 9) show that 56% of the exogenously elevated levels of CCK were extracted by the kidney over the 10-minute period. Urinary excretion of CCK was not measured in this study; only negligible quantities of gastrin are excreted via the urine.[4,36] The fate of CCK picked up by the kidneys is not known. It may be simply altered by the renal parenchymal cells and returned to circulation in an immunochemically unrecognizable form. It is likely that, as with gastrin, urinary excretion is not important. Grace and associates[12] have suggested that gastrin may be removed at least partially by direct uptake from peritubular blood, and CCK, because of its similar molecular conformation, may be handled in a similar fashion.

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DISCUSSION

DR. WILLIAM SILEN (Boston): I think Dr. Thompson has indeed validated an excellent assay for CCK. We certainly look forward to further studies from his very productive laboratory showing us the interactions between CCK, gastrin and soon perhaps even secretin.

I did note on some of his slides that the CCK concentrations were elevated for as long as six hours after a meal. I wonder whether Dr. Thompson has any data on the concentration of CCK at which we get physiologic effects in man. In other words, can we expect at those high levels to show how stimulation of contraction of the gallbladder or increase in pancreatic enzyme output perhaps that hasn't been studied yet.

It is of some interest that these levels are very high even at six hours.

Of particular interest, I think, are the elevations noted in the Zollinger-Ellison patients. Perhaps here we have another example of a tumor which might indeed elaborate in addition to gastrin, another hormone.

In the diabetic patients, I would ask whether there's any information on the gastric function of these patients since certainly the changes in CCK which were seen in the blood might reflect some changes in motility or secretion which is known to occur in diabetic patients.

Finally, do we have any evidence of the disappearance rate of what might be called big CCK since we know that big gastrin, for example, has a much longer half-life than normal or little gastrin.

Dr. James C. Thompson (Closing discussion): Dr. Silen asked why levels of CCK persist so high so long post-prandially and I don't know. I know the gastrin levels also persist for a long time post-prandially. It may well be that these levels are due to persistence of forms that are metabolically inactive.

For example, after a meal gastrin levels are high for a long time and yet gastric secretion falls off. We suspect that the persistence of these high levels is due to the protection from catabolism of the larger forms of gastrin which are still recognized by the immunoassay (big, big gastrin and a form of gastrin called by Rehfeld component I) apparently do not stimulate gastric secretion. They are apparently resistant to catabolism and yet they continue to be picked up by the radioimmunoassay. I think it will be necessary for us to learn to distinguish between molecular forms of these polypeptide hormones before we can correlate their radioimmunoassay levels of bioactivity.

He asked in what kind of levels in dogs and man do we see physiologic actions. In dogs we get gallbladder contraction and secretion of pancreatic enzymes at about 400 pgm. We have correlated these in dose response studies to intra-duodenally administered amino acids.

We have not done gastric function studies in these diabetic patients, but have studied other diabetic patients and have confirmed that, in general, diabetic patients show a slower pattern of gastric emptying and diminished gastric acid formation. Why they should have such a rapid rise in cholecystokinin is not at all clear. Duodenal ulcer patients of course have rapid gastric emptying. You would anticipate this liquid meal would get into the duodenum early and would cause release of cholecystokinin. Diabetic patients on the other hand tend to empty their stomachs slowly. All individuals empty liquids at a different rate than solids, as Keith Kelly has shown so many times. It may be that diabetics handle this liquid meal differently. We do not know that.

The next question was what is the half-life of a large cholecystokinin-39 or 39 amino acid form of cholecystokinin. I don't know.

I'm quite sure that we could extrapolate that endogenously, that is naturally released cholecystokinin will in all probability be a mixture of the various forms which have different rates of setting, physiologic mechanisms in the motion and also they have different susceptibility to catabolism.

The larger forms seem to be released more slowly, to be less biologically active, and to be more resistant to catabolism and they apparently function as sort of a reserve form.

No one has yet indicated that the larger forms of the molecules can be converted to the smaller forms in circulation, but they certainly must be converted in the mucosa.

Now, we have not been able to correlate some of these studies in dogs because of the peculiarity that we cannot secure the endogenous release of cholecystokinin in anesthetized animals, which, of course, frustrates any experiments we want to do acutely in dogs.

It's particularly strange since both secretin and gastrin and glucagon and calcitonin and almost any other polypeptide hormone is released at the same rate in the anesthetized animals as they are in asleep animals, yet with CCK, the release is blunted so that only about 10% of CCK—we only get about 10% release of CCK in animals that are asleep. That may have some particular significance about the mechanisms of release. They may be highly dependent upon exogenous innervation. We don't know that.

The Pathogenesis of Pulmonary Edema in Acute Pancreatitis

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Acute pulmonary edema appeared 3 or more days after the onset of acute pancreatitis in 7 patients, an approximate incidence of 8%. The severity of pancreatitis in these patients was characterized by massive requirements for intravenous colloid and by marked hypocalcemia. In addition, at least 5 of the 7 patients had very high serum levels of triglycerides at the time of hospital admission. Hemodynamic studies during pulmonary edema showed normal central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance. Cardiac index was appropriately elevated. Respiratory treatment, consisting of endotracheal intubation and controlled ventilation with PEEP, was successful in allowing reversal of the pulmonary injury and recovery of respiratory function within 1-2 weeks in all cases. Two patients died later from pancreatic abscesses. The findings indicate that a distinct form of pulmonary injury may occur in acute pancreatitis, characterized by loss of integrity of the alveolar-capillary membrane, leading to pulmonary edema. The mechanism of injury is not known but may be caused by circulating free fatty acids, phospholipase A, or vasoactive substances. The pulmonary membrane lesion appears to heal during the period of intensive respiratory support.

RESPIRATORY INSUFFICIENCY develops in up to 30% of patients with acute pancreatitis, due in varying degrees to pleural effusions, atelectasis, pneumonitis, diaphragmatic elevation, pain-induced splinting of the abdominal wall, and iatrogenic fluid over-load.[8,17,18,25,27,29] In addition to these factors and in part obscured by them, we believe that there is a distinct form of pulmonary injury in pancreatitis characterized by acute pulmonary edema. This report documents that the entity, "pancreatitis lung," is the result of an alveolar-capillary leak syndrome.

Clinical Materials and Methods

Each year approximately 135 patients with acute pancreatitis are admitted to the Massachusetts General Hospital. Of 60 unselected patients studied prospectively during one 9-month period, 5 developed pulmonary edema, an incidence of 8%. Observations made during 8 separate attacks of pancreatitis and pulmonary edema in 7 patients (including the 5 patients noted above) are the basis of this report.

Acute pancreatitis was diagnosed using standard clinical criteria and an elevated serum amylase. The primary identifiable etiologic factors were alcohol abuse (3), Type IV hyperlipoproteinemia (2), gastrectomy (1), and idiopathic (1). The diagnosis of pulmonary edema was made radiologically in patients with respiratory distress. Clinical management of pancreatitis consisted of nasogastric suction, antibiotics, and infusion of sufficient intravenous fluids, including colloids, to support blood pressure and urine output. Anticholinergic drugs were not used.

Evaluation of cardiac and pulmonary function included the following parameters: serial chest radiographs, arterial blood gas analyses, central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and cardiac index (CI). Pulmonary artery and pulmonary capillary wedge pressures were measured with the use of a flow-directed balloon-tipped (Swan-Ganz) catheter. Cardiac output was determined by the

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TABLE 1. *Admission Data*

Pt.	Age, Sex	Amylase (5-25 Russell u)	Calcium (8.5-10.5 mg%)	Triglycerides (40-150 mg%)	Pa_{O_2} (F_1O_2 = .21)	Chest Radiograph
1	45, M	143	7.5	1,450	79	clear lungs, normal heart
2	67, F	336	8.1	——	95	clear lungs, left ventricle enlarged
3A*	41, M	152	6.5	242	—	interstitial edema, normal heart
3B	41, M	141	7.1	1,960	76	clear lungs, normal heart
4	49, F	56	5.9	10,000	91	clear lungs, normal heart
5	62, M	68	6.5	——	—	clear lungs, normal heart
6	47, F	148	5.5	537	95	clear lungs, normal heart
7	38, M	42	9.3	435	70	clear lungs, normal heart

Normal values are given in parentheses
*transferred to MGH on 9th day of illness

dye-dilution method using indocyanine green. Pulmonary vascular resistance was calculated from the mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output.

Results

Initial status (Table 1)

At the time of hospital admission no patient was in respiratory distress, despite severe abdominal pain, nor was there evidence of pre-existing pulmonary disease. In each case, a radiograph of the chest showed clear lung fields, no pleural effusions, and normal heart size (with one exception). In all 6 cases in which it was measured on the day of admission, the Pa_{O_2} of arterial blood was greater than 70 torr while the patient was breathing room air. Serum lipids were markedly elevated to the point of visible lactescence in the 6 instances in which observations were recorded. This contrasts strikingly with an overall incidence of 11% for hyperlipidemia in all cases of acute pancreatitis seen during the study period. Serum calcium was below normal in 7 of 8 cases, and was less than 7.0 mg% in 4 of those.

Clinical course

In every case large amounts of 5% albumin in saline were administered intravenously to support blood pressure and urine output at acceptable levels (Table 2). The total colloid volume given in the first 24 hours after admission averaged more than 3400 ml. Generally the need for such fluid therapy was much reduced in the second 24 hours (average, 600 ml of colloid); yet respiratory distress appeared 48-96 hours after admission. Chest radiographs now showed interstitial fluffy infiltrates in a distribution characteristic of pulmonary edema, but heart size did not increase (Fig. 1). Small pleural effusions were present in one-third of the patients, but in none was there a large pleural effusion or major elevation of the diaphragm. Serial Pa_{O_2} measurements indicated progressive hypoxemia (Table 2). All patients required endotracheal intubation and controlled ventilation for respiratory sup-

TABLE 2. *Onset of Pulmonary Edema*

Pt.	1st 24 hrs	24 hrs before intubation	Pulmonary edema, day of intubation	Pa_{O_2} (F_1O_2 = 1.0) after intubation and PEEP
1	6000	6000	2	53
2	2000	500	3	94
3A*	——	——	8	——
3B	3000	500	3	51
4	1500	500	3	260
5	2000	700	3	80
6	5000	800	3	62
7	4750	500	4	132

*transferred to MGH on 9th day of illness.

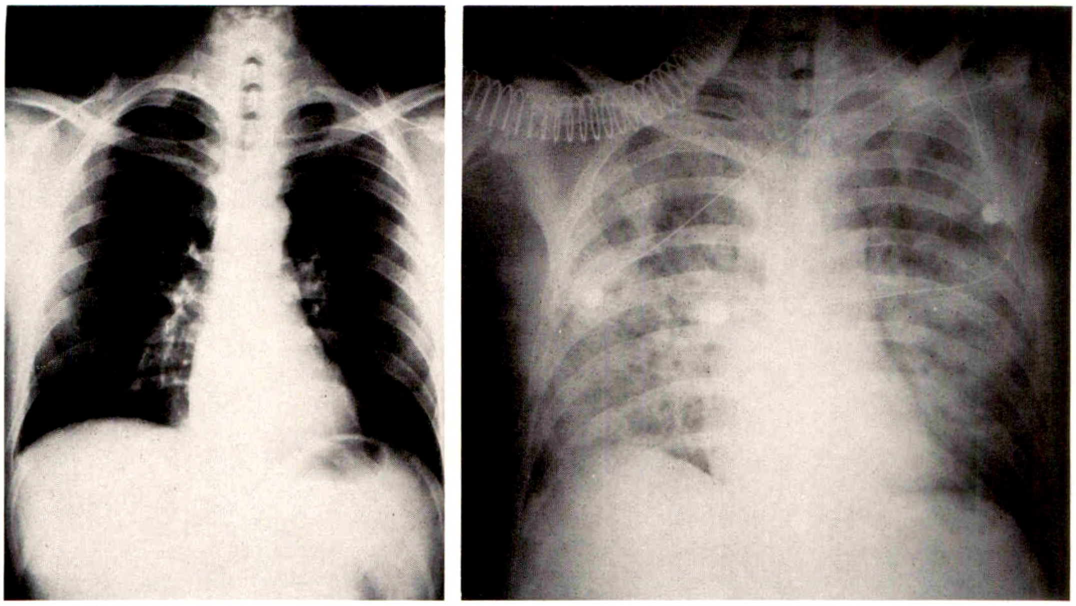

FIG. 1. Radiographs of the chest (patient 3) on admission (left) and on the 3rd hospital day (right), after endotracheal intubation for acute pulmonary edema.

port. Positive end-expiratory pressure (PEEP) was applied in most instances. Examination of the sputum did not yield evidence of infection at the time of intubation.

Special studies

Table 3 contains the pertinent measurements of cardiovascular function. All patients were normotensive at this time. The CVP, PAP, PCWP, and PVR were normal throughout, despite moderate to severe pulmonary edema. CI in each case was high, a normal physiologic response to stress and fever.

In one case sufficient pulmonary edema fluid was present to measure its protein content: the total protein concentration in the edema fluid was 5.4 gms per 100 ml while the serum protein was 5.6 gms per 100 ml.

Outcome

Continuous positive pressure ventilation was necessary for an average of 7 days (range, 3-14 days). PEEP was used routinely to increase functional residual capacity and to allow reduction of the inspired oxygen concentration required for adequate arterial oxygenation. Without PEEP arterial P_{O_2} invariably decreased. No specific attempt was made to extract pulmonary water by the combination of raising serum protein concentration and diuresis.[31]

Five of the 7 patients survived these 8 episodes of pancreatitis and pulmonary edema. Both deaths (patients 2 and 6) were directly due to the development of pancreatic abscesses and occurred on the 37th and 40th hospital day. All 5 survivors, including patient 3 who survived two such attacks of pancreatitis and pulmonary edema, had clinically normal pulmonary function upon discharge.

Discussion

The recognition that respiratory distress is a common feature in acute pancreatitis has led to a number of recent reports emphasizing the roles of pneumonitis, atelectasis, and congestive heart failure.[7,15,27] It is clear from these reports, furthermore, that respiratory distress may become the predominant therapeutic problem of acute pancreatitis and may prove to be lethal.[8,10,25,27] While pleural effusions, restriction of chest and diaphragmatic movement, and infection certainly contribute to respiratory failure in this disease, some patients (8% in our experience) develop unequivocal acute pulmonary edema, a phenomenon which has received little attention.[7,10,15,18] Pulmonary edema appeared several days after the onset of pancreatitis and was of sufficient severity to necessitate endotracheal intubation and positive-pressure ventilation.

The major pathogenetic mechanisms of pulmonary edema are: 1) increased hydrostatic forces (congestive heart failure), in which left atrial hypertension leads to passive increase in the pulmonary vascular pressures with *transudation* of fluid into the pulmonary interstitium. When the rate of transudation exceeds the resorptive capacity of the pulmonary lymphatics, alveolar flooding (pulmonary edema) occurs. 2) Disruption of the alveolar-capillary membrane with secondary *exudation* of protein-rich plasma into the pulmonary interstitium in the presence of normal or decreased hydrostatic forces.[28,32] In the patients we have studied, the evidence strongly suggests the latter set of circumstances. The normal CVP, PCWP, and heart size, despite the fact that these values were obtained during positive-pressure ventilation with PEEP, exclude heart failure, whether due to fluid overloading as a conse-

TABLE 3. *Hemodynamics During Pulmonary Edema*

Pt.	CVP (2-10 cm H_2O)	PAP (15-28/5-15 torr)	PCWP (4-10 torr)	PVR (<2 resistance u)	CI (3-4 L/min/M^2)
1	5	—	—	—	5.8
2	10	15/5	10	—	—
3A	6	—	—	—	—
3B	3	30/11	11	1.0	6.0
4	8	30/10	5	—	—
5	4	25/15	7	1.6	4.1
6	11	—	—	—	5.8
7	10	—	—	—	—

Normal values are given in parentheses

quence of intravenous therapy or to underlying heart disease. The appropriately elevated CI is inconsistent with inadequate myocardial performance, which theoretically could be related to a circulating myocardial depressant factor (MDF) found in experimental pancreatitis.[21,22] Additionally, the elevated protein concentration of the pulmonary edema fluid in one of our patients, almost equal to the serum protein concentration, indicates an exudate, different from the transudate typical of cardiogenic pulmonary edema wherein the protein content is about 40% of the serum protein level.[16] Finally, the normal PAP excludes pulmonary hypertension, which has been reported in acute pancreatitis[13] and which has been postulated to give rise to pulmonary edema via leak from pulmonary arterioles.[36]

The specific agent of the alveolar-capillary membrane injury is unknown, although liberated pancreatic enzymes,[2,9] vasoactive substances,[12,24,30,33] platelet microemboli,[3] and endotoxins[32] are candidates. A particularly attractive hypothesis holds that phospholipase A, a lecithinase released in acute pancreatitis,[37] destroys phospholipid components of the pulmonary membranes, including surfactant. This chain of events has been reproduced in dogs,[23] but its existence in man is speculative.

The relationship between hyperlipidemia and pancreatitis is complex and probably not uniform.[4-6,11] In some cases hyperlipidemia pre-exists and predisposes to pancreatitis; in others it appears only during the acute attack and may be either a consequence of pancreatitis or may be a simultaneous product of a shared process which causes both the pancreatitis and the hyperlipidemia. The extraordinary incidence of hypertriglyceridemia in our patients with pulmonary edema suggests more than a chance association. One possibility is that the elevated triglycerides are metabolized to large quantities of free fatty acids, which in experimental models can damage the alveolar-capillary membrane and produce pulmonary edema.[1] Unfortunately we have no measurements of plasma free fatty acids.

The serum lipids also seem to be the single best index for risk of developing pulmonary edema. At least 5 of the 7 patients (during 6 of 8 episodes) had markedly elevated triglycerides, an observed incidence far exceeding the 11% incidence of hyperlipidemia in our pancreatitis patients or even the 15-39% incidence in other series.[4,6,11] Large requirements for intravenous colloid infusions (possibly indicating widespread increased vascular permeability) and marked depression of serum calcium concentration were also characteristic of these patients but may simply reflect the severity of their pancreatitis.[18,26,27,35] In contrast, clinical respiratory status, x-ray examination of the chest, and arterial blood gas measurements at the time of hospital admission were of no use in predicting pulmonary edema.

The cornerstone of treatment for this form of pulmonary injury is endotracheal intubation with controlled ventilation in order to keep alveoli and small airways open. PEEP in our experience was regularly effective in improving oxygenation and in thereby facilitating the reduction of inspired oxygen concentrations below toxic levels. We made no attempt "to extract pulmonary water" with salt-poor albumin infusions and diuresis,[31] as has been advocated for respiratory failure in pancreatitis.[15,18,27] If damage to the alveolar-capillary membrane has rendered it excessively permeable to protein, infusion of concentrated albumin could not osmotically draw edema fluid from the lung and might theoretically add to the protein exudate.

The membrane injury in acute pancreatitis appears to be reversible: no patient died from respiratory failure, and the 5 ultimate survivors of 6 episodes had no apparent residual lung damage. The aim of treatment therefore is intensive respiratory support and prevention of pulmonary infection during the time necessary for pancreatitis to subside and for the membrane to heal. Steroids have been suggested to promote healing of the damaged lung[14] but their efficacy in this setting is unproven.

Patients who develop pulmonary edema have virulent pancreatitis in other respects as well. Although respiratory failure may become the predominant and longest-lasting feature of the attack, massive volume requirements, profound cardiovascular collapse, renal failure, disseminated intravascular coagulation,[19] and profound hypocalcemia occur and demand treatment as well. However, contrary to previous tentative conclusions,[20,27,35] respiratory failure, because of its ready response to supportive treatment, should not be used as a criterion for surgical intervention, peritoneal lavage, or peritoneal dialysis. Pancreatitis of this severity carries a high risk of a consequent pancreatic abscess,[34,35] which occurred twice in this series and was the direct cause of both deaths.

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DISCUSSION

DR. JOHN RANSON (New York, New York): Dr. Warshaw's presentation describes fascinating new observations on the pulmonary manifestations of pancreatitis.

We recently analyzed our experience at Bellevue Hospital with respiratory complications in 116 patients with acute pancreatitis. We found that some degree of respiratory impairment was detectable by arterial blood gas measurements in 69% of patients during the initial 48 hours illness. This early arterial hypoxemia was not related to the severity of disease nor to any of the laboratory or clinical features that we studied at that time.

Clinically apparent respiratory complications, which included the type of patient presented by Dr. Warshaw, could be related to the presence of severe or continuing pancreatic inflammation. As shown on this slide, they were thus related to early hypocalcemia and fluid sequestration, as described by Dr. Warshaw, and also to age and to early operation. I wonder whether the association with hyperlipidemia reported in this presentation may not also simply reflect the severity of the underlying pancreatitis.

Clinically apparent respiratory complications were also related to the initial serum amylase levels, supporting the suggestion that circulating pancreatic enzymes may play a part in their pathogenesis. So far, in a small number of patients and in animals, we have been unable to demonstrate a relationship between detectable circulating phospholipase A levels and respiratory failure.

Another pancreatic enzyme found in the blood of patients with pancreatitis is trypsin, which produces marked changes in blood coagulability. A common pathological feature in the lungs of these patients is the presence of fibrin thrombi such as the one shown on this slide. We therefore studied the relationship between early arterial hypoxemia and coagulation factors in 33 patients. There was no clear relationship between platelet counts and arterial Po_2, but initial mean fibrinogen and fibrin-related-antigen levels were significantly higher in those patients who became hypoxemic, suggesting a possible relationship between the coagulation changes which have been reported in pancreatitis and respiratory failure.

In summary, we believe some degree of respiratory impairment is common in most patients with pancreatitis. Severe respiratory failure appears to reflect severe or continuing pancreatic inflammation or the effect of early laparotomy. There is some evidence that coagulation abnormalities may be involved in the pathogenesis of the respiratory changes. I would like, therefore, to ask Dr. Warshaw if he has any data on the coagulation status of his patients.

DR. PAUL NEMIR, JR. (Philadelphia): I rise to corroborate the findings of Dr. Warshaw and his group and to mention another possible causative factor. The refractory nature of the pulmonary complication is impressive and is another consideration that points to something other than the usual factors implicated in pulmonary insufficiency. The following chest roentgenogram demonstrates this. This was a patient admitted to the hospital with severe acute abdominal pain of about 30 hours duration. While pancreatitis was suspected, a clear diagnosis could not be made and exploration was carried out around 12 hours after admission to reveal a severe hemorrhagic necrotizing pancreatitis with considerable bloody peritoneal fluid. The chest roentgenogram on admission was not remarkable, but this film, taken on the day following operation, revealed this homogenous density consistent with pulmonary edema. With the most intensive supportive management this gradually cleared as shown on these slides at three days and nine days after admission. At about 13 days after admission, chest x-ray was essentially normal. This slide shows the blood gas determinations. The reinsertion of the endotracheal tube was necessary upon recovery from anesthesia and positive pressure ventilation and tracheostomy also became necessary. You will note that it was only after about nine days that there was substantial improvement in the gas analyses. We have felt also that a toxic circulating substance is released in hemorrhagic necrotizing pancreatitis. Our concept has been that hemoglobin or plasma proteins are denatured by the pancreatic enzymes and at some stage in the breakdown to amino acids lethal substances are formed. I might add that we still have the continuous help and guidance of Dr. Drabkin in this aspect of the study. Among substances that we have studied has been alkali denatured hemoglobin. As demonstrated on this slide, injection of small amounts of this material causes a fall in the systemic pressure, a decrease in the cardiac output, but especially a very significant increase in the pulmonary vascular resistance. Control animals were injected with a protein of similar molecular weight, known to be resistant to denaturation, brought to a pH of 10.8 prior to injection. The latter substance had no effect on the cardiac output or the blood pressure or the pulmonary vascular resistance. The histologic picture in the lungs of these animals is similar to that seen in the shock lung with pulmonary edema, focal atelectasis, and interstitial hemorrhage.

I would like to ask Dr. Warshaw if he would comment on the other six patients that survived. In every instance, when we have noted this really severe pulmonary insufficiency, it has been in association with acute hemorrhagic necrotizing pancreatitis as determined either at operation or autopsy. I wonder is he could tell us, with respect to the six, whether they were operated upon or whether there was other evidence that there was a necrotizing pancreatitis.

DR. ANDREW L. WARSHAW (Closing discussion): Dr. Ranson and his associates at Bellevue have contributed a great deal to the knowledge of respiratory insufficiency in pancreatitis over the last two or three years. I would like to point out that their experience, their group of patients, as they have described them, is different. Dr. Ranson has carefully pointed out in his writings that none of his patients developed pulmonary edema. These are patients, by and large, with the other manifestations of respiratory insufficiency, the other causes and perhaps a different group than we have tried to select out here today.

Dr. Ranson asked whether the association of hyperlipemia might not be simply an association with severity. We have had a continuing interest at the Massachusetts General in very severe pancreatitis and have selected out the particularly severe patients for operation. In this particular group of patients, who have the most severe pancreatitis that we can identify, the incidence of hyperlipemia is about the same 11 or 12% that exists in our overall group. There appears to be no relationship with severity, per se.

The mechanisms and relationships of hyperlipemia to pancreatitis are rather diverse. In some cases, as in two of the patients listed here, there is a familial or predetermined form of hyperlipoproteinemia (type four in our two patients) which perhaps gives rise to the pancreatitis.

In many other circumstances, the hyperlipemia does not appear except at the time of pancreatitis. Whether it is caused by the pancreatitis or whether the two different phenomena are caused by the same common ancestral factors, I think we simply do not know. The association remains intriguing and incompletely understood. In addition, in our experience there is a high correlation of high risk of patients who present with hyperlipemia going on to develop pulmonary edema.

Dr. Ranson also mentioned his observations upon alterations of blood coagulation and of production of platelet thrombi. In his experimental model, a close approximation of the shock lung model as Dr. Blaisdell has recently reviewed it, pulmonary vascular resistance characteristically is elevated. PVR is characteristically not elevated in our patients with pulmonary edema. We have seen decreased platelet levels in three of our patients, but they appear to be associated with dilution by enormous infusions of albumin and not simply consumption.

I might mention that we originally postulated that respiratory failure may be a reason for operating on such patients early or for peritoneal dialysis. Our present experience underlines the fact that the respiratory failure due to pulmonary edema is perfectly reversible without the need for operation. Hence, we have backed away from this as a criterion for operation or peritoneal dialysis, and now use the cardiovascular effects of pancreatitis as our primary criterion.

Dr. Nemir mentioned his experimental model using denatured proteins or alkaline denatured hemoglobin. Here again we're talking about a model that produces increased pulmonary vascular resistance and that therefore appears to be a different phenomenon than what we have observed.

Of the six patients who survived, only one underwent an operation. Both patients who died had evidence of pancreatic abscesses, which is certainly an excellent indication in my opinion that they had severe necrotizing pancreatitis. However, we have observed, as has Dr. Ranson, that respiratory failure may far outweigh and predominate over all other problems during the illness and may be the lethal factor in what otherwise is perfectly controllable pancreatitis.

Risk of Recurrence of Colon Polyps

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CHARLES APRAHAMIAN, M.D.,§ JEROME J. DECOSSE, M.D.**

At Wood Veterans Administration Center, 268 patients who had a polypectomy have been followed up to 20 years with semiannual proctosigmoidoscopic and barium enema examinations. For the present review of benign polyp disease, patients having coexisting carcinoma, chronic inflammatory disease, and those lost to followup have been excluded; 154 patients followed for a mean of 7 years comprise the study group. Thirty per cent of patients developed recurrent polyps. The risk of recurrence during the first year was 16 times that expected in a population of similar age and sex, but thereafter diminished steadily. After 48 months risk of polyp recurrence was little higher than the incidence expected in a normal population. Neither patient age, presenting symptoms nor the site or size of the initial polyp(s) were of any prognostic value regarding recurrence. Patients presenting with a villous adenoma or with more than 3 polyps had a significantly increased risk of recurrence. Among patients who had developed a recurrent polyp, one-third developed another recurrence. In this subgroup, although numbers are small, the risk of developing further recurrence may persist indefinitely. The overall incidence of colonic carcinoma may have been increased, but the location of subsequent cancer was not related to the site of a previously excised polyp.

From the Surgical Service, Wood Veterans Administration Center, and The Division of Surgery, The Medical College of Wisconsin, Milwaukee

INITIAL THERAPY of a polyp of the colon or rectum is aimed at polypectomy and establishment of an exact histologic diagnosis. How often, and for how long, should a patient be re-examined after removal of a benign polyp of the colon or rectum? The number of such patients is appreciable and increasing yearly as proctosigmoidoscopic and fiberoptic colonoscopic examinations are used more frequently.

Knoerschild[8] ingeniously tatooed polyps and noted that most remained dormant or disappeared; less than 1% underwent malignant degeneration. Studies by Castleman[4] and by Spratt, Ackerman and Moyer[14] have taken the view that cancers arise de novo or in villous adenomas but not in adenomatous polyps.

Although much of the evidence is circumstantial, the works of Bacon and Peale,[2] Dockerty,[5] Welch et al.[16] and Morson,[10] support the hypothesis that colon polyps are premalignant lesions. Weakley and Swinton,[15] Koppel et al.[9] and Prager et al.[11] have suggested that polyps herald a diffusely abnormal colonic mucosa and have recommended lifetime re-examination for all patients with colorectal polyps.

To obtain information which might resolve these diverse viewpoints, a prospective study was conducted during 1954-1974 at the Veterans Administration Center, Wood, Wisconsin, into which every new patient with a

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TABLE 1. *Study Population.*

Patients with Polypoid Lesions		268
Less Exclusions		
Coexisting Carcinoma	47	
Multiple Polyposis	10	
Crohn's Disease	1	
Polyp Not Confirmed	15	
Lost to Follow-up	41	
Study Population		154

TABLE 2. *Histology of Initially Excised Polyp.*

	A No Recurrence	B Recurrence
Adenomatous Polyp	63%	56%
Adenomatous Polyps with Atypia or CA in situ	24%	26%
Villous Adenoma	3%	12%
Other Benign Diagnosis	10%	6%

polypoid lesion of the colon or rectum was entered, regardless of the presence of other associated disease. The protocol called for semiannual proctoscopic and barium enema examinations performed by surgical and radiology house staff.

Methods

A polyp was defined as any mass lesion arising from mucous membrane and proven by histologic examination. Data were transferred to punch cards, verified, and tabulated. The basic questions were: 1) are there any determinants of predictive value concerning recurrence; 2) is there any time interval during which polyp recurrence is likely; 3) do patients with recurrent polyps need extensive re-examination, and 4) what is the incidence of subsequent carcinoma?

Of 268 patients entered, 237 were available for review. Patients who on initial diagnosis had coexisting carcinoma, multiple polyposis, Crohn's disease, lacked biopsy proof of the nature of the initially observed polyp, or lacked at least one followup visit were excluded (Table 1). One-hundred-fifty-four patients remained and comprise the study population.

Patients were followed for up to 20 years. Those having no evidence of a recurrent polyp comprise Group A. Those in Group B developed a recurrence, defined as any polyp not seen on initial examination and subsequently excised and histologically confirmed. Differences between Groups A and B were tested for significance using the Chi-square test.

Clinical Findings

Ninety-six per cent of the patients were Caucasian males, reflecting our Veterans Hospital population. Their ages ranged from 21 to 82 with a mean of 58 years; ages were evenly distributed in Groups A and B. Nearly half the patients had symptoms referable to the gastrointestinal tract but not necessarily due to the polyp. One-third

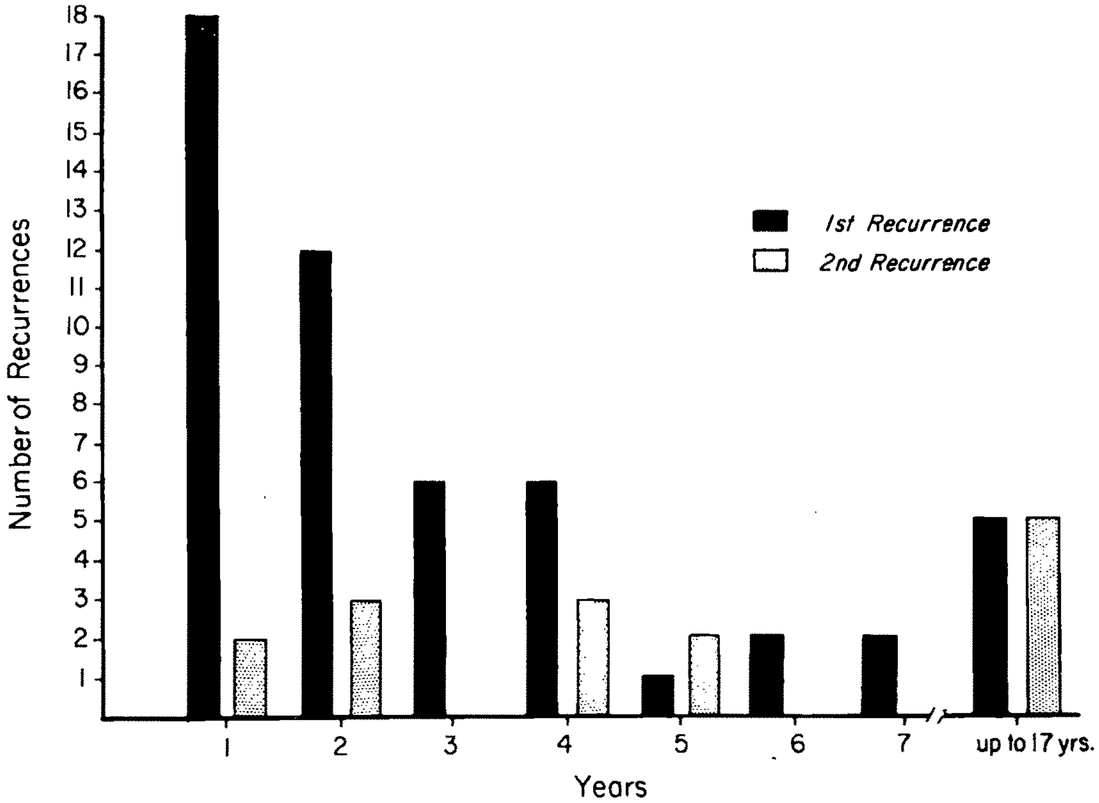

FIG. 1. Incidence of first and second polyp recurrences.

had a history of lower gastrointestinal bleeding. The frequency of gastrointestinal symptoms did not differ in Groups A and B. Most polyps were discovered and removed transrectally; transabdominal colotomy was required in 22 patients.

All patients had neoplastic polyps[10] with or without foci of atypia or in situ carcinoma. None demonstrated invasion of the polyp stalk. Adenomatous polyps comprised the majority of initial and recurrent polyps. Nevertheless, 24% of Group A and 26% of Group B polyps demonstrated either atypia, carcinoma in situ, or carcinoma without stalk invasion (Table 2). Of polyps removed, 24% were described as sessile and 62% as pedunculated; the remainder were not classified. Three-quarters of both initial polyps and of recurrences were noted in the distal 25 cm of the colo-rectum. Polyps removed usually were small; 78% were 2 cm or less in diameter. Recurrent polyps also were small; 83% had a diameter of 2 cm or less.

At initial examination, 114 patients had one polyp removed; 17 patients had two polyps removed, 5 had three polyps removed, and 10 had more than three polyps removed but did not have multiple polyposis (Table 3). Fifty-two of 154 patients (30%) developed a recurrent polyp, a finding in general agreement with preceding studies.[3,6,12]

Plotting recurrences against time (Fig. 1) indicates that most recurrences are within 48 months of initial diagnosis. This observation prompted life table analysis of our data. Fig. 2 graphically compares the incidence of polyp recurrence in our study population with polyp prevalence in an age adjusted general population.[1,7]

Of the 52 patients with a recurrent polyp, 15 (29%) had yet a second recurrence. The number of patients with second recurrences is too small to permit life table analysis; but it appears that following a second recurrence, liability to further recurrences may persist indefinitely (Fig. 1).

Statistical analysis indicated that the following features were of no value in predicting polyp recurrence: gross appearance, size, site, patient age or symptoms. Two features were associated with recurrence: an initial diagnosis of villous adenoma, and excision of more than 3 polyps at the initial examination.

Four patients developed carcinoma of the colon. One patient who developed cecal carcinoma had had a rectal polyp excised at the 5 cm level two years previously. Two patients who developed sigmoid carcinomas above 25 cm had had polyps removed at 15 cm, the first two months earlier, the second two years earlier. Only one patient developed carcinoma in the locality of a previously excised polyp; this patient developed sigmoid carcinoma 10 years following removal of an adenomatous polyp.

TABLE 3. *Effect of Number of Polyps Initially Excised on Subsequent Polyp Recurrence.*

No. Polyps Removed	A No Recurrence #	%	B Recurrence #	%
1	82	72	32	28
2	10	59	7	41
3	2	40	3	60
>3	2	20	8	80

Discussion

If a polyp of the colon or rectum is found during the course of examination, what constitutes a rational approach to re-examination? In our study, once a diagnosis of noninvasive neoplastic polyp was confirmed, 30% of patients developed a recurrent polyp. Life table analysis revealed an increased risk of polyp recurrence during the first 48 months after initial polypectomy (Fig. 2). Periodic proctoscopic and barium enema examinations during the 4 years following polypectomy will permit identification and excision of most recurrent polyps. Subsequently, the risk of further polyp recurrence is no higher than polyp prevalence in the population at large.

It would appear from our data that some undefined stimulus to continued polyp formation persists for up to 4 years in about one-third of patients who develop a colon polyp. Thereafter, either the stimulus to neoplasia is no longer present, or the colonic mucosa adapts so that polyp formation does not persist. However, in a smaller sub-group of patients, defined by the development of a third polyp, the neoplasia promoting stimulus is not lim-

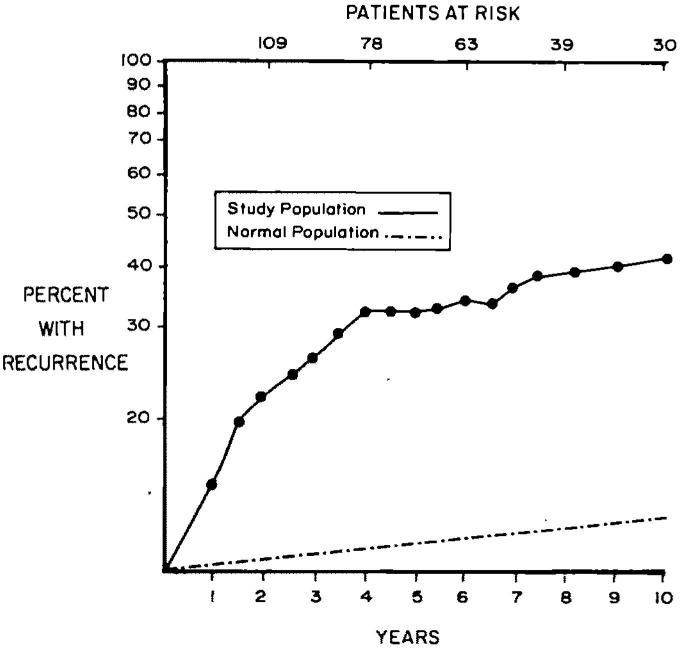

FIG. 2. Life table data of polyp incidence in a normal population compared to first polyp recurrence in our study population.

ited and may persist indefinitely. We can only conjecture about possible mechanisms to account for this intriguing observation.

The age specific incidence of carcinoma of the colon and rectum for a group of patients comparable to ours is 90 per 100,000.[13] Our 154 patients, studied for a mean of 7 years, comprise an 1100 patient-year cohort in which one would expect only one carcinoma to develop. In fact, 4 patients in our study developed a carcinoma. In one, the cancer appeared two months after the polypectomy in a geographically different site; this case probably represents a missed diagnosis. The other three patients developed cancer 2, 2 and 10 years following polypectomy. Only one patient developed a carcinoma in the same geographical location as a previously removed polyp. Although the number of patients is small, the cancer incidence is three times that expected. Nevertheless, the period of excess cancer risk, as well as of excess polyp recurrence risk, appears to be the 4 years following polypectomy.

Conclusions

Patients with a benign polyp have a 30% chance of developing a recurrent polyp. The risk of developing a new polyp is 16 times that of the general population at 12 months, but after 48 months rapidly approaches that of the general population. The presence of villous adenoma or of more than 3 polyps at initial examination were factors associated with an increased incidence of polyp recurrence. Patient age or complaints and the size or site of the polyp were of no prognostic value. Thirty per cent of patients with recurrent polyps will have a second recurrence.

Acknowledgments

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DISCUSSION

DR. CLAUDE WELCH (Boston): Dr. Henry attempts to answer a question that has troubled us for many years and I'm sure that if you, as I did myself, will look up your followup results of the polyps you have treated you will find that you have been quite remiss in doing what should have been done.

It was about 15 years ago that Dr. Moyer convicted us of slaying polyps; at present we are not only slaying polyps, we are beginning to take out a hunting license to go after them a little while longer. And, if we're going to take out a hunting license, one can get the license for a certain length of time; this is what he has specified because four years appears to be the proper time at which one can find most of these recurrences or new polyps.

Or a second method would be to get a license for certain types of animals. Thus it is very tempting to say that the same features that one uses to decide whether or not a polyp is benign or malignant in the first place could be applied to determine whether or not a second polyp will develop after the first one has been removed.

Now, those items are four in number. They refer to the size, the presence or absence of a pedicle, the presence or absence of a villous adenoma, and the number of polyps that are present.

Dr. Henry has focused on two of these points and proved if there are over three polyps, or if a villous adenoma is present, that the chances of a new polyp are greater; consequently these are the patients who should be followed most closely.

Perhaps a further analysis of his material might show that the other two factors are likewise of importance. Dr. Wolff touched upon these two features in his paper. For example, the presence of a sessile polyp may eventually turn out to be much more important than emphasized by Dr. Henry. Furthermore, if various sizes of polyps are considered, the answer could be different.

For example, if one took the cutoff figure at a half centimeter (which would eliminate all of the hyperplastic polyps) or perhaps at one centimeter, the figures might be quite different from the two centimeter level that was chosen. Size of the original lesion may be a very important feature in determining whether or not careful follow-up should be carried out.

DR. RICHARD WARREN (Boston): About 20 years ago we followed a series by sigmoidoscomy and barium enema and found exactly this same incidence of recurrence, so-called. About half were not recurrence, but polyps, new polyps arising very near the old site. This is, of course hard to prove, but we developed the concept, which I'm sure is not original, that the mucosa of these colons is polyp-bearing or has a tendency to polyp formation, in general.

What is the magic about the four years? We cannot argue with the facts presented, but there's something that seems strange about this. I would appreciate any philosophical thoughts Dr. Henry might have on why the tendency should cease at four years. It seems to me that he gives us a little too much of a sense of security using a number like this to control our followup length of time on any patient who has a tendency to polyps.

DR. ROBERT E. CONDON (Closing discussion): Dr. Welch pointed out there were possibly four elements relating to recurrence; the presence or absence of villous adenoma, site and size of the polyp and whether or not it had a pedicle.

As you'll remember from Dr. Henry's presentation, we found that villous adenoma was a predictor of recurrence. As regards site and size, you'll remember site didn't and neither did size. We had eliminated from entry into this study patients who did not have true neoplastic polyps so that no patients with metaplastic or juvenile polyps which are not neoplasms, entered this study. This automatically removes from consideration a lot of patients who have little small mucosal excrescences of absolutely no clinical significance.

The remaining feature about pedicle, about 60% of patients both in the recurrence and in the no recurrence groups in our study had a pedunculated polyp and this was not of predictive value in identifying those who were liable to recurrence.

Dr. Warren has indicated that the presence of polyps and certainly the presence of recurrence would indicate a general predisposition on the part of the colonic mucosa to the development of neoplasms and I think we would share that view.

I don't think that we can push the data of our study beyond the information that we have given you. Of those patients in our study who developed a first recurrence, about a third developed a second recurrence. We're now talking about 15 patients. In that group, although most of them occurred in the first four years, the numbers are so small and they do continue to trickle on that we're really unsure about whether this small subset is in some fundamental way different from the general polyp population. The small subset may have a continuing tendency toward neoplasia.

Why four years? I don't know. As an interesting speculation, if there's a stimulus to neoplasia, it would appear that at least in the majority of patients it is either short-term or certainly lasts for no longer than four years. As an alternative, perhaps the mucosa becomes adapted to whatever neoplastic stimulus is present. That's an even more interesting and fascinating concept, but we have no data.

Definitive Treatment of "Malignant" Polyps of the Colon

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There has been an unremitting rise in incidence of colonic cancer in this country with no recent improvement in cure rate. As a result the evolution of colorectal cancer has been the focus of considerable attention with an enlarging body of evidence pointing to the common neoplastic polyp as a precursor to malignancy. "Neoplastic" polyps include "adenomatous polyps," "villous adenomas" and, lately recognized, "villo-glandular polyps." Experience with endoscopic removal of over 2,000 colonic polyps (with no mortality) has introduced two questions of prime concern to the surgeon: (1) What constitutes *clinical* malignancy in a polyp? and, (2) When should laparotomy supplant or follow endoscopic removal? Eight hundred and ninety-two consecutive adenomatous (tubular), villous, villoglandular (villo-tubular) and "polypoid cancer" polyps are analyzed, 855 of which have been followed for 6 months to 4 years. Support is offered to the concept that villous and tubular growth patterns are merely variants of a similar base disturbance in cell renewal. Superficial cancer (carcinoma-in-situ) occurred in 6.6% of neoplastic polyps and represents no threat if the polyp is completely removed. Only when the cancer penetrates the muscularis mucosae should it be regarded as "invasive." The term "malignant polyp" should be reserved for this form. Invasive cancer was found in 5.0% of neoplastic polyps in this series. Only in this group need the question of further surgical intervention be raised. Major considerations influencing a decision for subsequent laparotomy are polyp size and gross morphology (i.e. sessile or pedunculated), histologic type (of the polyp and of the cancer itself), adequacy of clearance between depth of invasion and plane of polyp resection, and the patient's age and general condition. These are analyzed. Twenty-five of 46 patients with "malignant polyps" were subjected to abdominal exploration: 17 showed no residual cancer, whereas 8 (5 with recognized incomplete endoscopic removal) had tumor in the bowel wall. Of the remaining 21 patients, for whom endoscopic polypectomy alone was deemed appropriate, none have shown residual or recurrent cancer on clinical and endoscopic followup. Colonoscopy appears to be a most promising approach in terms of the goals of cancer programs, offering both prophylaxis and opportunity for treatment at a favorable stage of disease.

EXPERIENCE with endoscopic removal of over 2,000 colonic polyps has enabled us to focus on two questions of concern to surgeons: 1) What constitutes "clinical" malignancy in a polyp? 2) When should laparotomy supplant or follow endoscopic removal?

One factor contributing to confusion is vocabulary.[1,2,5,11,14,16,22,25] A lack of clarity and consistency exists in the use of terms by both clinicians and pathologists, not only among themselves but also in communicating with each other. The literature contains numerous examples of the application of the same or similar terms applied to difference entities and of a multiplicity of names for the same thing.[11]

If we accept the concept that a polyp is "any lesion protruding from a flat surface"[14] then Table I is a listing which includes most of the lesions considered among colorectal polyps, and the terms commonly applied to them.

Considerable controversy exists with respect to the *frequency* with which colonic polyps show cancerous change.[28] However, there is reasonable agreement among pathologists that the only polyp-like lesions in the above groupings which have any real malignant potential are the true neoplasms, i.e., those subsumed under the general heading "adenomas."[5,19,22]

Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

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TABLE 1. *Colorectal Polyps*

Hyperplastic	metaplastic, mucosal
Adenomas*	
Tubular	adenomatous polyp
Villous	papillary adenoma, papilloma
Villotubular	villoglandular or mixed polyp
Juvenile	congenital, retention
Peutz-Jeghers	
Inflammatory	lymphoid; pseudopolyps; etc.
Polypoid Carcinomas	

*Malignant potential.

Strong evidence is offered by Lane et al.[5,15] and by Morson et al.[22] supporting the view that real and significant biologic differences exist with respect to cellular behavior in hyperplastic (or metaplastic) polyps as opposed to the adenomas. Hyperplastic polyps, which usually appear as small dome-shaped lesions (Fig. 1) are thought to constitute 90% of all colorectal polyps.[5] By excluding these alone from consideration the picture becomes considerably clearer with respect to the frequency and anatomical distribution of large bowel polyps. Moreover, it is claimed that hyperplastic polyps have no significant role with respect to malignant potential.[5,15,17,22] Our own studies of the large bowel based on over 5,000 colonoscopies, confirm the frequency and innocuous nature of these growths.

Thus, we gain much ground by focusing on the true neoplasms or adenomas in terms of a polyp-cancer sequence. Adenomas appear in all sizes and shapes and have the histologic and cytologic attributes of true tumors.[5,12,22] Moreover, despite a not uncommon belief that adenomatous polyps and villous adenomas are quite separate and distinct, the view that these two forms are, fundamentally, the same disease process is now supported by many authorities.[3,5,7,11,12,22] Although villous tumors often assume the configuration of large sessile growths, they possess a stalk much more frequently than is generally appreciated (Fig. 2). Further proving a close relationship between the two forms is the frequent occurrence of mixed growth patterns in the same polyp. Recognition of this has led to acceptance of a third category known as mixed or villoglandular polyps[3,13,14,22,29,31,34] (Fig. 3). To avoid confusion we have adopted the modified terminology shown below, which will be used in this report (Table 2). Our material consists of 892 polyps endoscopically resected, 855 of which have been followed for a minimum of 6 months.

TABLE 2. *Polyps*

Juvenile Polyp = Retention Polyp
Hyperplastic Polyp = Metaplastic Polyp

Tubular Adenoma = Adenomatous Polyp
Villous Adenoma = Papillary Polyp
Villotubular Adenoma = Villoglandular Polyp
Polypoid Carcinoma = Malignant Polyp

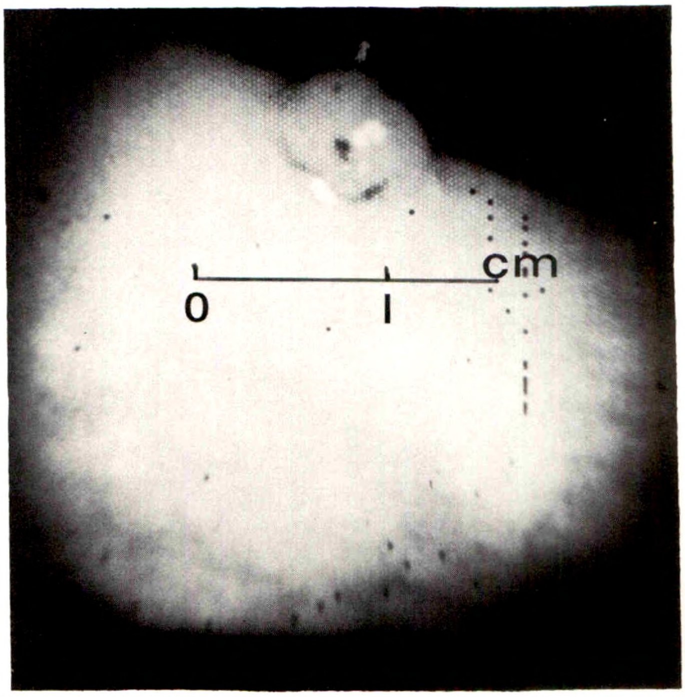

FIG. 1. Hyperplastic polyp seen through the colonoscope.

Our experience supports the contention that a villous or papillary growth pattern is associated with an increased malignant potential,[10,13,14,22,35] a widely accepted concept (Table 3). In terms of endoscopic resection, however, the gross morphology of the lesion, i.e., its size and shape and the presence or absence of a stalk, may have as much direct bearing on definitive management as the histologic characteristics (vide infra).

If we eliminate from consideration the non-neoplastic polyps, and accept as a fact that a very close biologic relationship exists in the neoplastic or adenoma subgroups, then a third matter of importance is to establish unambiguous criteria of what is being referred to by the

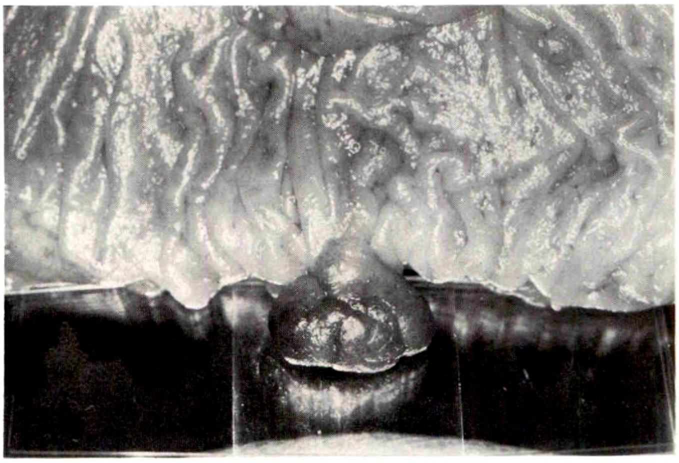

FIG. 2. Villous adenoma with wide stalk.

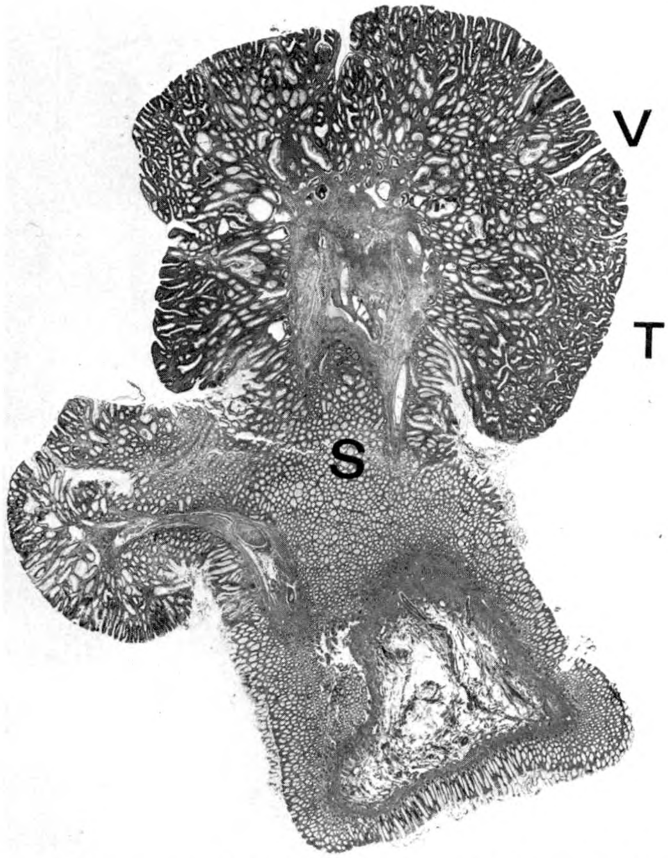

FIG. 3. Photomicrograph of villotubular polyp. (Tubular area T; villous area V.) Stalk (S) is covered by normal mucosa.

TABLE 3. Colonoscopic Polypectomy Neoplastic Polyps

Histopathology	No.	Invasive CA (%)
Tubular Adenoma	511	3.3%
Villotubular Adenoma	260	3.8%
Villous Adenoma	111	12.6%
Polypoid Carcinoma	10	100.0%
Total	892	

term "malignancy" or "cancer" in a polyp. There is a near concensus among pathologists on the following issues: 1) The "earliest" (least advanced) form in which colorectal carcinoma can be recognized is intramucosal carcinoma (carcinoma in situ); 2) Intramucosal carcinoma rarely occurs in normal mucosa but is common in adenomas; 3) Purely intramucosal carcinoma has never been known to metastasize;[5,11,22,25] 4) A polyp with carcinoma in situ will behave like a benign lesion provided it is completely removed; 5) Invasion through the muscularis mucosae is the best criterion for malignancy in the clinical sense (Fig. 4); 6) Whenever possible, reports on malignancy in colorectal polyps should differentiate between invasive and non-invasive or in-situ cancer, because this is the decisive feature with respect to clinical management.

All of the above considerations play a large role in the wide disparity relating to the reported incidence of malignancy in colonic polyps as it appears in the literature (Table 4).

Comparison of findings as shown above has only lim-

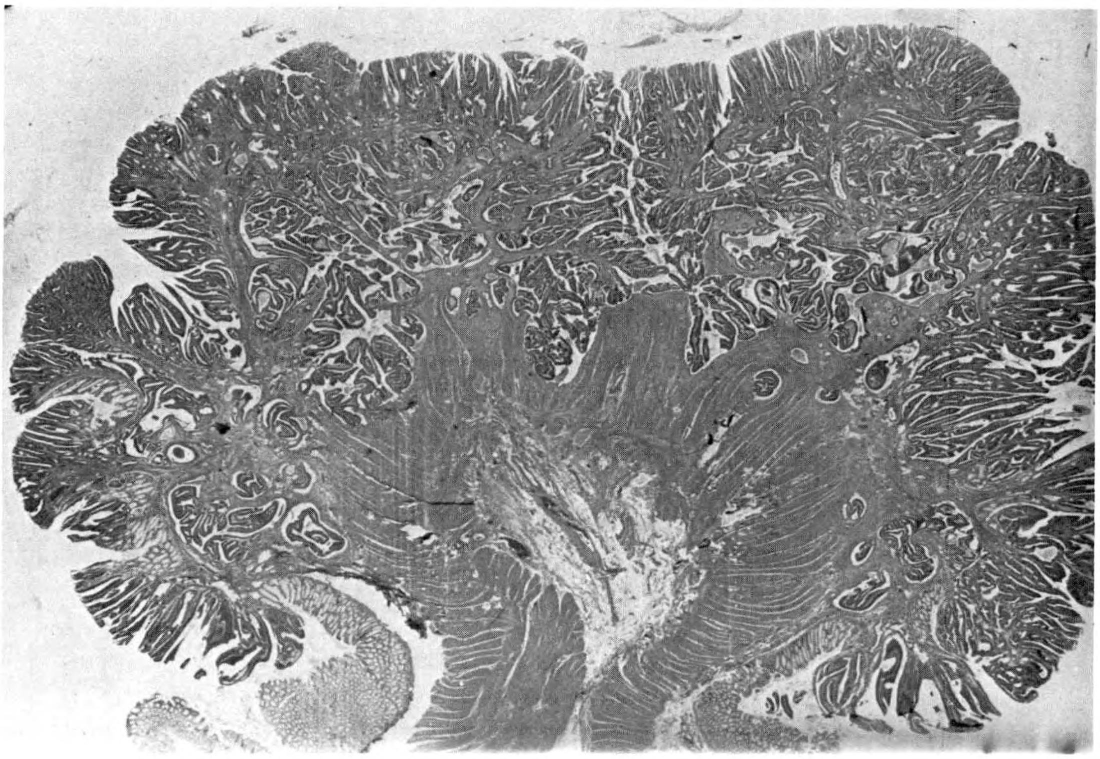

FIG. 4. Photomicrograph of pedunculated polyp with cancer cells penetrating the muscularis mucosae.

TABLE 4. Reported Incidence of Malignancy in Colorectal Polyps

	No. Cases	Overall	Ca in situ	Invasive
Spratt et al. (1958)	425*	?	9.9%	0.2%
Grinnell & Lane (1958)	1856	?	?	6.3%
Silverberg (1970)	500	14.0%	?	?
Kurzon (1974)	662	14.0%	11.2%	2.9%
Kaneko (1972)	458*	9.4%	1.1%	8.3%
Enterline et al. (1962)	1700	?	?	5.8%
Wolff & Shinya	1019	10.8%	5.8%	5.0%

*Adenomatous polyps only.

ited usefulness because of bias in sampling. Source of material is one example, data based on autopsy material differing from that obtained from surgical specimens (particularly if the polyps analyzed occurred in bowel segments resected for associated frank cancer). Our own material, based on colonoscopic examination, has a relative paucity of low-lying lesions since these cases tend to be treated by proctologists and are infrequently referred to us.[34,35]

It is apparent then, that without a clear understanding of what a report of "malignancy" means, we cannot discuss treatment on common grounds. Electron microscopy has shown that lymphatics do not exist in the mucosa,[4] so carcinoma in situ cannot gain entry to the lymphatic system and therefore cannot metastasize. The natural history of such lesions *un*treated, however, is not known, for once removed the polyp can no longer give evidence with respect to its malignant potential. There is strong indirect evidence that favors a sequence of dysplasia—carcinoma in situ—invasive cancer. Also that many years may pass before such polyps evolve into frank cancer.[5,20–23,27]

Treatment

In practice we subscribe to the concept that complete removal of polyps with carcinoma in situ is an effective cure. We know of no proven recurrence in such circumstances. Endoscopic polypectomy offers the opportunity for careful and unhurried examination of the specimen by the pathologist. This is a great improvement over frozen section study of a polyp removed at colotomy with the surgeon standing by, impatiently awaiting the result. Completeness of removal of polyps via the colonoscope depends on the expertise of the endoscopist and the gross morphology of the tumor, particularly whether it is sessile or pedunculated and the dimensions of the stalk when present. Very large polyps (over 5 cm in diameter) or broad flat lesions may not lend themselves to endoscopic removal and we recommend laparotomy in such cases, except under exceptional circumstances. Most, but not all, broad flat lesions are villous adenomas. Either a villous architecture or large size is known to be associated with an increased incidence of invasive cancer.[10,19,22,27,33–35] Transabdominal removal seems prudent for most of these cases (Fig. 5). Over-ambitious efforts via the colonoscope are not wise. On the other hand, neither is a policy of non-operative conservatism warranted when based on a negative colonoscopic biopsy report with these types of lesions: random biopsy samples are small and may not be representative. Moreover, we have had the experience of removing large lesions on a piecemeal basis at sequential sittings only to have invasive cancer reported after a series of entirely benign reports.

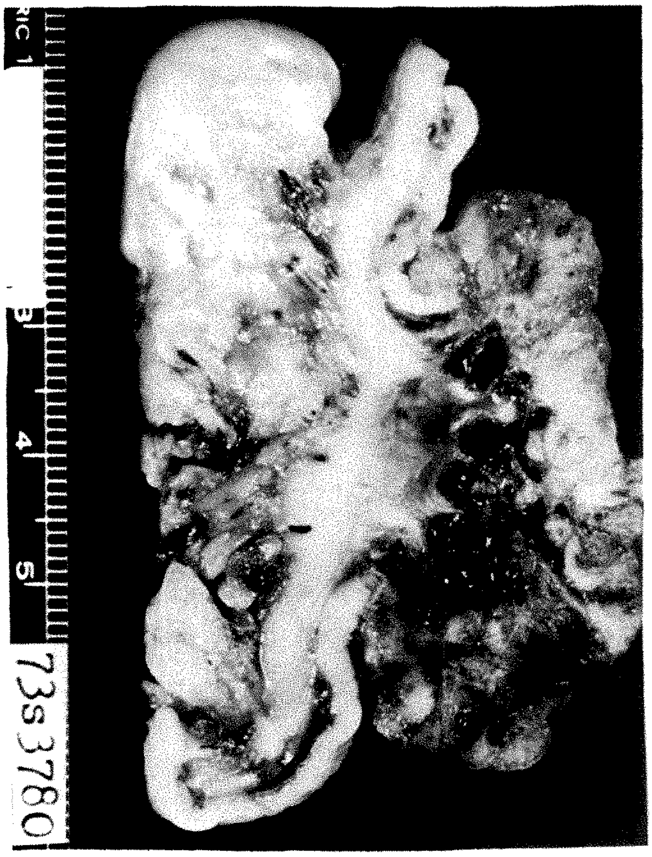

FIG. 5. Large villous adenoma in sigmoid colon. Partial excision via colonoscope reported as benign. Surgical specimen showed invasive cancer.

Analysis of our case material with respect to category and incidence of malignant change is shown in Tables 5 and 6.

In Table 7, 46 malignant polyps are analyzed according to the adenoma subgroup to which they belong, to size, and to gross morphology. These malignant polyps, all removed prior to October 1974 form the basis of the present report.

Table 8 provides similar data for the entire group from which the previous were drawn.

These figures differ in a number of respects from older published reports because endoscopic polypectomy, as mentioned, lends itself best to removal of smaller and

TABLE 5. *Colonoscopic Polypectomy–Neoplastic Polyps: Histopathology and Incidence of Malignancy**

Histopathology		Malignancy	
		Ca in situ	Invasive
Tubular Adenoma	511 (57.3%)	21	17
Villotubular Adenoma	260 (29.2%)	27	10
Villous Adenoma	111 (12.4%)	11	14
Polypoid Carcinoma	10 (1.1%)	—	10
	892 (100%)	59 (6.6%)	51 (5.0%)

*To 12/31/74.

pedunculated lesions and least well to large sessile tumors. However, what is of interest is proof that invasive cancer can and does occur in small polyps with surprising frequency (Table 9): invasive cancer was found in 13 tubular adenomas, 3 villotubular adenomas and 5 villous adenomas under 2.0 cm in greatest diameter. Also 6 of 8 polypoid carcinomas fell into this size range. Moreover, 4 polyps with invasive cancer were under 1 cm in diameter. The clear magnified view through the colonoscope of a well-cleansed air-inflated colon or rectum often permits ready detection of smaller lesions. Many observers have noted the relatively slow rate of growth of polyps.[6,20,21,30] Unfortunately, we do not know whether growth rate, expressed as doubling time, is altered by the appearance of malignant change. However, it has been suggested that failure of a polyp to grow can be regarded as evidence of benignity.[6] Conversely, there has been documentation of the fact that the growth rate of some entirely benign adenomas may duplicate the growth behavior of a carcinoma.[6]

With respect to gross morphology, it is of interest to note that invasive cancer was found in 13 out of 127 sessile polyps (10.2%) as opposed to 33 out of 728 pedunculated polyps (4.5%) (Tables 10 and 11). This is in accord with known facts and has obvious implications in terms of attempts at endoscopic removal.

While the colonoscopist can be quite acute in his evaluation of the configuration of *smaller* polyps (provided, of course, they are not missed) we have experienced a number of limitations of a technical nature with respect to *larger* lesions which we feel should be brought to the attention of those attempting colonoscopy or interpreting the reports of the procedures done by others. On occasion, even the most experienced endoscopist may be in error in evaluating large growths, either because they partially block the lumen or his field of vision. Thus, lesions thought to be sessile sometimes prove to be pedunculated at subsequent examination, or after laparotomy and segmental colonic resection. Also, polyps considered to have been completely excised, in a few instances, may prove subsequently to have been only partially removed. Hence, as we have stated before, early endoscopic followup examination is important after endoscopic polypectomy for those patients who are not booked for abdominal exploration.

Pedunculated polyps: Polyps with long stalks tend to be tubular or villo-tubular adenomas (Fig. 6). Length permitting, under optimal circumstances the stalk should be transected about 1 cm from the colonic wall, tenting being carefully avoided. A cardinal rule in snare-cautery removal of polyps via the colonoscope is never to release the snare once it is tightened down:[26] therefore, the polyp is not always "lassoed" at an optimal level. Once removed, prompt fixation and proper orientation by the pathologist is advisable to permit coronal sectioning. If, on microscopical examination, cancer cells are found penetrating the muscularis mucosae, then, and *then only,* in our opinion, should the lesion be called a "malignant polyp." Infrequently, the muscularis mucosae is not clearly defined, rendering judgment difficult; artefactual errors also must be avoided as counseled by Castleman and Krickstein.[1,2] With the exceptions to be noted below, polypectomy alone appears to be adequate for such malignant polyps.

Re-examination of the polypectomy site is scheduled after a 6 to 12 week interval and periodically thereafter.[26] In this series there were 15 such polyps with no known recurrences after a followup of 6 months to 4 years.

A more aggressive attitude is suggested for malignant polyps with a sizable pedicle if any one of 3 special conditions exists: 1) penetration of cancer cells close to the plane of resection—and we are unable to state what is

TABLE 6. *Colonoscopic Polypectomy: Malignant Change in 892* Neoplastic Polyps*

	With CA in situ	*%of Group	Invasive Cancer	*% of Group	Total %
Tubular Adenoma	21	2.4%	17	2.0%	4.4%
Villotubular Adenoma	27	3.0%	10	1.1%	4.1%
Villous Adenoma	11	2.8%	14	1.6%	4.4%
Polypoid Carcinoma	—	—	10	1.1%	1.1%

a safe margin in numerical terms; 2) cancer cells in the lymphatics (Fig. 7); and 3) the cancer itself is poorly differentiated—a rare occurrence.[22]

A comment is in order with respect to reports of metastases from malignant pedunculated polyps in which only the head of the polyp appeared to be involved. This has created a good deal of unwarranted concern in the minds of surgeons. A careful review of the literature reveals only 21 documented cases of this type.[25] In these at least one of the above-mentioned conditions was present. No such case has been encountered in our experience. It is a rare phenomenon.

In this pedunculated group there were 11 polypectomy cases in which abdominal exploration was carried out after the endoscopic procedure. In 3 of these incompleteness of polypectomy was noted at the time it was done and, these were the only patients in the group whose resected colon segments showed residual disease. Thus, among the remaining 8, despite the fact that cancer coming close to the plane of resection was the indication for further surgery in several, none showed residual tumor. Nevertheless, we still regard this pathologic finding as a strong indication for operative followup.[27]

There is little accurate information on the long term results of treatment of adenomatous polyps with malignant changes. A recent report by Shatney et al.[24] supports our current policy.

Sessile polyps. Many so-called sessile polyps actually have short stalks *(Fig. 2).* Sometimes this fact is best appreciated by the endoscopist who examines a bowel which is inflated and whose mucous membrane lining is flattened. The absence of a stalk makes more difficult but does not preclude endoscopic resection. One hundred and twenty-seven of 855 polyps (14.8%) over 0.5 cm in diameter endoscopically resected were regarded as sessile (Table 9).

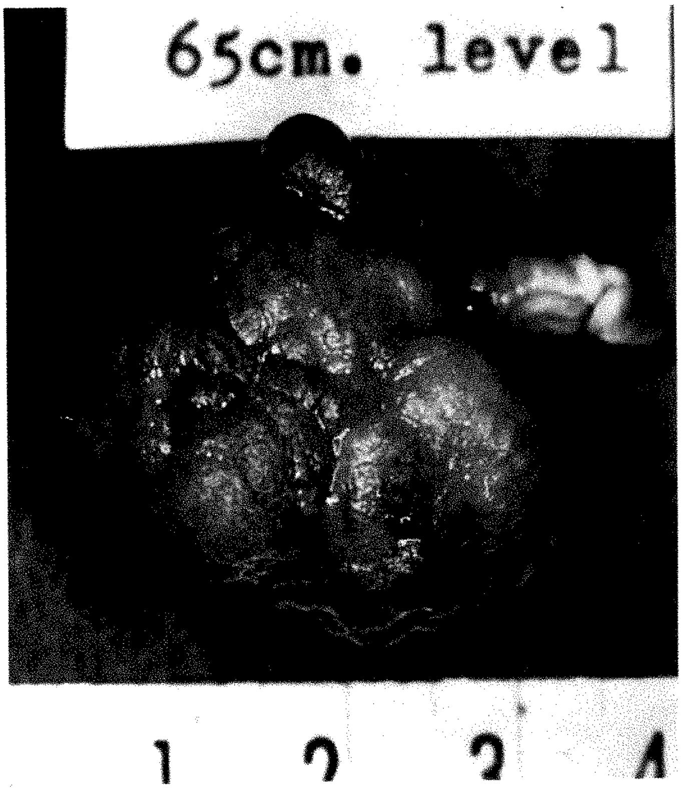

FIG. 6. Pedunculated tubular polyp resected from descending colon via the colonoscope.

Often all sessile lesions are thought of as being villous adenomas. While this was true to a certain degree in our material the differences were not striking since only 20.1% of villous adenomas were classed as sessile as opposed to 15.3% of tubular adenomas and 11.6% of villotubular polyps.

Our finding of 79.8% of villous adenomas with pedicles coincides with the observation that villous adenomas are more frequently pedunculated than generally appreciated,[22] but it is still considerably greater than the 10% figure quoted by Welch.[29] We are unable to account for this discrepancy adequately. A number of possible

TABLE 7. *Gross Morphology of Neoplastic Polyps: With Invasive Cancer Endoscopically Resected**

Polyp Classification	Number	Size (cm)	Configuration	
			Sessile	Pedunculated
Tubular Adenoma	16	<2	4	9
		2-3	1	0
		>3	0	2
Villotubular Adenoma	8	<2	1	2
		2-3	0	2
		>3	2	1
Villous Adenoma	14	<2	1	4
		2-3	2	4
		>3	1	2
Polypoid Carcinoma	8	<2	1	5
		2-3	0	2
		>3	0	0
Total	46		13	33

*To 10/1/74

TABLE 8. *Gross Morphology of Neoplastic Polyps Endoscopically Resected*

Polyp Classification	Number	Size (cm)	Configuration	
			Sessile	Pedunculated
Tubular Adenoma	489	<2	66	341
		2-3	8	55
		>3	1	18
Villotubular Adenoma	249	<2	18	127
		2-3	7	68
		>3	4	25
Villous Adenoma	109	<2	8	41
		2-3	7	25
		>3	7	21
Polypoid Carcinoma	8	<2	1	5
		2-3	0	2
		>3	0	0
Total	855		127 (14.9%)	728 (85.1%)

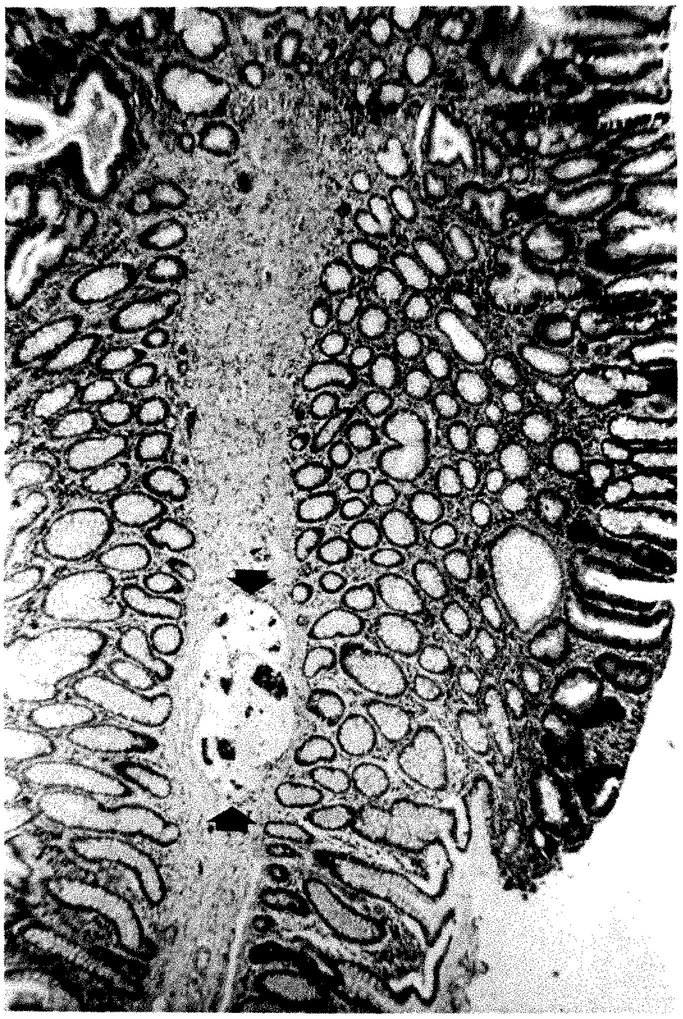

FIG. 7. Photomicrograph of malignant polyp with cancer cells in lymphatics of stalk.

explanations may be offered: (1) Most polyps we see on colonoscopy are beyond the range of the conventional sigmoidoscope whereas villous adenomas are said to occur more often in the rectum and sigmoid colon.[9,10,18,19] Goldfarb[9] found villous adenomas of the right colon "smaller than . . . noted by some." (2) Broad flat villous adenomas do not lend themselves readily to endoscopic excision. (3) Reported figures may be in error, small pedunculated polyps being called adenomatous polyps out of habit and larger sessile ones, villous polyps. Perhaps more emphasis should be placed on Morson and Bussey's statement with respect to villous adenomas: "The presence or absence of a stalk is irrelevant to the diagnosis."

TABLE 9. *Invasive Cancer in Polyps Under 2 cm Diameter*

Tubular Adenomas	13
Villotubular Adenomas	3
Villous Adenomas	5
Polypoid Carcinomas	6
Total	27

TABLE 10. *Gross Morphology and Invasive Cancer*

	Total	% With Invasive Cancer
Sessile	127	10.2%
Pedunculated	728	4.5%

In this series 13 of 127 sessile polyps showed the presence of invasive cancer. Five of these were tubular adenomas, 3 villotubular, 4 villous, and 1 a polypoid carcinoma. In 4 of the 13, endoscopic removal was not followed by laparotomy and there has been no recurrence on followup re-examination in any of these. In 9 laparotomy was carried out. In 2 it was known that endoscopic removal had been incomplete. Of the remaining 7, 3 had residual cancer in the subsequently resected colon. One of these last 3 arose in a malignant tubular adenoma, one in a villotubular polyp, the third in a purely villous lesion. In only one were lymph nodes involved and this patient had had 7 piecemeal snare-cautery excisions of an 8 cm villous adenoma before invasive cancer was reported in the specimen.

It is apparent that until more is learned about the subject, most sessile lesions endoscopically removed should be followed by laparotomy if invasive cancer is reported, regardless of the histological pattern. This is in keeping with the principles of cancer surgery in general, namely adequate clearance in 3 planes.

Polypoid carcinoma. By definition this is a malignant polyp in which no trace of a pre-existing adenoma can be demonstrated (Fig. 8). Among the 8 in this series 7 had a stalk and 6 were under 2 cm in diameter, as noted *(Table 9)*. In all, the diagnosis of cancer was only suspected at the time of snare-cautery excision. Without doubt this is a highly selected group for polypoid cancers of larger size are more easily recognized as such: they would, therefore, be biopsied rather than excised via the colonoscope and, hence, would not be included in the series.

Our policy has been to recommend laparotomy when the resected polyp proves to be a polypoid carcinoma. Very interestingly, our data do not support this for, among the 5 patients in which this was done, *none* were found to have residual cancer. Moreover, of 3 not operated upon, none has had evidence of recurrence or metastasis, 2 having been followed for 2 years, and 1 for 6

TABLE 11. *Sessile Polyps Endoscopically Resected*

Subgroup	Number	% of Entire Subgroup
Tubular Adenoma	75	14.7%
Villotubular Adenoma	29	11.2%
Villous Adenoma	22	19.8%
Polypoid Carcinoma	1	12.5%
Total	127	

months. A larger experience and longer followup is required for this group.

Discussion

Long term studies show the prophylactic value of polypectomy via the sigmoidoscope.[8,24] If these can be reproduced using the colonoscope for lesions beyond this range, it can be anticipated that endoscopy will contribute immensely toward reducing the mortality from cancer of the colon, assuming a low endoscopic morbidity rate. In addition, established cancers can be detected and diagnosed and, possibly, definitively treated at a more favorable stage of the disease than has heretofore been the custom. These are the goals of all cancer programs.

Conclusion

The newly developed technique of endoscopic excision of colorectal polyps has focused attention on definitive management when the resected polyp proves to be "malignant."

Past experience in terms of polyp management as reported in the literature is rendered confusing by lack of clarity and inconsistency of terminology. This is particularly true with respect to the "malignant polyp."

There is an enlarging body of evidence favoring a polyp-cancer sequence. This appears to occur predominantly, if not only, in those polyps which are truly neoplastic.

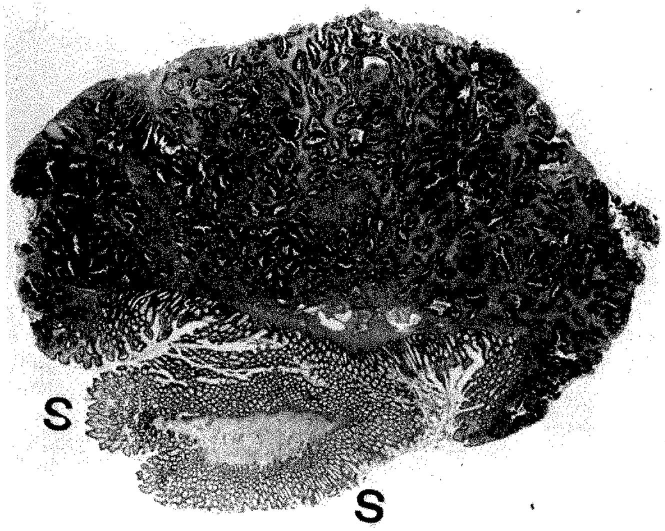

FIG. 8A. Photomicrograph of polypoid carcinoma. Stalk (S) is covered by normal mucous membrane.

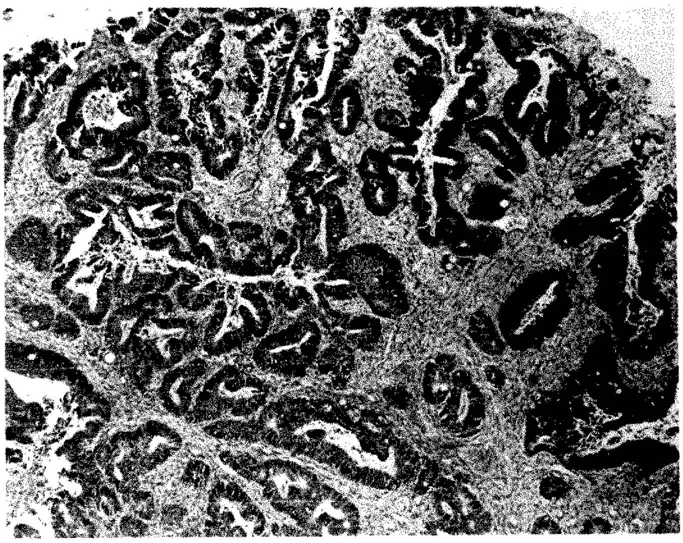

FIG. 8B. Higher power field of previous, showing well-differentiated infiltrating adenocarcinoma.

The least advanced form of cancer recognizable is intramucosal carcinoma or carcinoma in situ. This never metastasizes. Complete polyp removal is all that is required for such lesions.

The best criterion for polyp malignancy in a clinical sense is penetration of the muscularis mucosae. This constitutes invasive cancer. All reports on "malignant polyps" should clarify this factor whenever possible.

The present report includes an analysis of 892 neoplastic colorectal polyps endoscopically removed, 855 of which have been followed for a minimal period of 6 months. 6.6% had carcinoma in situ and 5.0% showed invasive cancer.

Invasive cancer arose with greatest frequency in villous adenomas (12.6%), next in villotubular adenomas

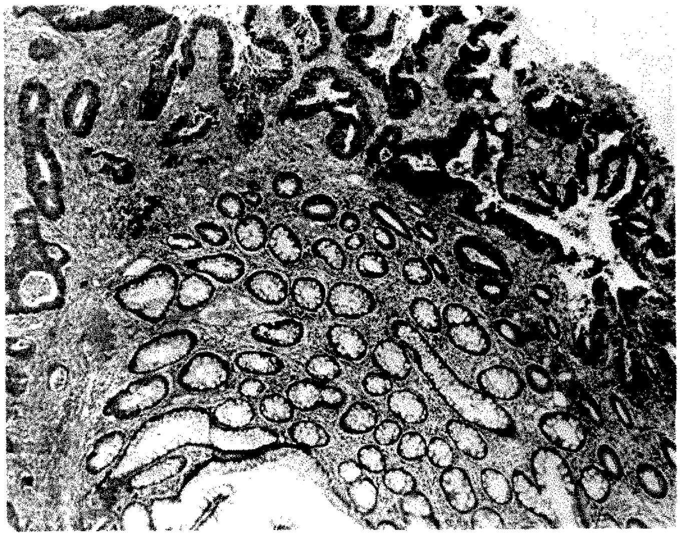

FIG. 8C. Junctional area of polyp and stalk, showing infiltrating carcinoma above, and normal mucous membrane below.

(3.8%), and least in tubular adenomas (adenomatous polyps) 3.3%. However, tubular adenomas were encountered with greatest frequency among the neoplastic polyps (57.3%), villotubular adenomas intermediate (29.2%) and villous adenomas least (12.4%). In addition, there were 10 polypoid carcinomas (1.1%).

We support the contention that villous and tubular growth patterns are merely variants of a similar basic disturbance in cell renewal and found villous adenomas to be considerably more frequently pedunculated than has generally been appreciated. Also, sessile lesions are more common among tubular adenomas than usually realized.

Invasive cancer appeared to be more frequent in larger lesions and those with a sessile morphology. However, 27 of 46 polyps with invasive cancer were under 2 cm in greatest diameter.

Endoscopic resection appears to be adequate therapy for pedunculated polyps with invasive cancer in the head unless: 1) the cancer is close to the plane of resection; 2) cancer is found in the lymphatics; or 3) the tumor is highly undifferentiated.

Sessile lesions with invasive cancer showed a higher incidence of residual tumor on subsequent colectomy than pedunculated lesions. Incompleteness of endoscopic resection appeared more closely related to gross morphology than to histological architecture, which is in keeping with general principles of cancer surgery calling for adequate clearance in 3 planes. Large sessile tumors should not be resected endoscopically except under exceptional circumstances.

Polypoid carcinomas resected and followed were small, pedunculated (7 of 8) and appeared to lend themselves well to endoscopic removal.

Colonoscopy appears to be an immensely promising modality in terms of the goals of cancer programs, i.e., prophylaxis, and detection and treatment at the most favorable stage of disease.

Acknowledgment

The authors are indebted to Dr. Richard Stenger, Director of Pathology; Dr. William Ober, Dr. Ada de Chabon and Dr. Ken Mori, Attending Pathologists, for their invaluable assistance.

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DISCUSSION

DR. WILLARD JOHNSON (Boston): As a part-time colonoscopist, with less experience than Dr. Wolff and his colleagues, I have awaited and certainly enjoyed his presentation about the treatment of these malignant polyps.

In a smaller series, we've had six patients who had extension of their carcinoma into the muscularis area. We chose to resect the colon in these six patients and none of them had any residual carcinoma in the specimen. Fortuitously, none of the patients have had any difficulty. But I think there is a problem as to when one might watch these endoscopically or when one might resect them.

I'd like a little more information, if possible, about the criteria as to what to do in the situation of muscularis invasion.

I'd also like advice from Dr. Wolff concerning patients with chronic ulcerative colitis whom one is following serially with endoscopic evaluation. Now they start growing polyps, and you've taken out two or three adenomatous polyps, what do you recommend at this stage? Does one continue doing serial endoscopy or when might colon resection be done.

DR. WILLIAM I. WOLFF (Closing discussion): Perhaps the four year interval has some significance because a study of the age group of onset of polyps and that of carcinoma of the colon shows that the cancer patients have about a 4–5 year older age difference on the average.

In terms of Dr. Johnson's query about when to do a laparotomy, I think one of the things we are convinced about is not to do a laparotomy if you have carcinoma in situ and it's non-invasive. This applies provided you have removed the whole polyp. This is rather easy to identify in terms of polyps with a pedicle; but in terms of the sessile lesion the best way to be sure is to re-examine the patient by colonoscopy. This we do after an interval of somewhere between six and twelve weeks.

In terms of sessile lesions, I think that our data show the presence of invasive cancer in these is of more ominous import than in pedunculated adenomas; this is, in general, in keeping with principles of cancer surgery in that you try to remove a lesion with adequate clearance in three planes. Therefore, I would be more inclined to explore the patient who has a sessile lesion showing invasive cancer.

As I mentioned, surgeons have been misled by the occasional reports of carcinoma in the head of a pedunculated polyp which have metastasized. Such metastasis is apt to occur only when the pedunculated polyp shows cancer down to the line of resection or if it's a very highly undifferentiated cancer, which is extremely unusual in polyps. Only under those circumstances do we feel that exploration is required for pedunculated polyps containing cancer.

With respect to his question about chronic ulcerative colitis, we do find adenomatous polyps in this disease, but generally when you remove the polyps in such cases these polyps are found to be inflammatory or hyperplastic.

I think colonoscopy offers an opportunity to discover early the presence of cancer in patients with chronic ulcerative colitis. I don't know how frequently you should examine them in order to discover this. I would suspect once a year might be a good interval.

I am concerned, however, about the fact that you can't rely on x-ray alone to disclose the presence of additional polyps or of carcinoma. In a comparison of colonoscopy with the barium enema in our experience we found about a 70% increment in the number of polyps discovered on colonoscopy over those that had been discovered on the barium enema examination.

Report on the Manpower Subcommittee

FRANCIS D. MOORE, M.D.

I SUPPOSE this is the Last Breakfast of SOSSUS; I do not see Leonardo in the balcony, to paint the picture. Dr. Zuidema and our President, Dr. Muller, have given you an excellent picture of the Study. I would like to add my own gratitude to this Association, to Dr. Zuidema, and to his staff, particularly Mr. George Sideris, for all they have done to help, and to the devoted group of workers in our committees, particularly those in our Department of Preventive Medicine, who have devoted full-time to this project for approximately five years. Dr. Osler Peterson, Miss Rita Nickerson, Dr. Theodore Colton, Dr. Walter Hauck, Dr. Klim MacPherson, and Mr. Bernard Bloom have made the Area Studies and Questionnaire possible.

However, that has turned out to be only one part of the Manpower Report, so much of the data of which you will see in the summary and then in the Long Form which will be printed this coming Fall. I wish to thank a small group in our own Surgical and Biophysical Laboratories, particularly Ms. Bogden, who have written the computer programs, derived all the manpower statistical data, the population rate analysis, specialty data on surgical and non-surgical fields, and worked out the predictive programs on which the manpower goals are based.

It is also appropriate here to indicate that the Committee on Issues, appointed last year by President Scott and President Muller, has held its first meeting and is now reviewing the completed SOSSUS data, to look at the future of these findings and these recommendations, and report on them to this Association annually.

I. Three Interlocking Recommendations

Three major recommendations stand out as preeminent, as based on data from the Manpower Study. These three interlocking concepts are ones for which we all must press hard both in our own communities, in the national surgical establishments, in the national medical societies, and in legislation. These three concepts apply to all of the specialties of American medicine and not to surgery alone. The surgeon, as always, has a high profile and will again take a leadership role in firmly establishing these three concepts.

The three concepts are mutually dependent and inseparable. They are as follows: 1) Manpower goals with realistic residency constraints and monitoring of residency output; 2) Hospital staff standards and the establishment of each hospital's obligation to maintain strict credentials for surgical privileges; 3) Continuing education, re-examination and the establishment of continued fitness.

I will not elaborate on the second and third items this morning, because I wish to concentrate on the matter of manpower goals. But I should emphasize that it is fruitless to have manpower goals without improved credentialling; by the same token, it is impossible to ask the public for the operational monopoly implied by credentialling, without recognizing our societal obligation for

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Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

high standards of postgraduate education, reexamination, and some sort of re-certification process.

II. The Need for a Continuing Data Base

Before looking at the Manpower goals, we should consider the data on which they are based. Manpower goals in surgery or in the other specialties should be confined to those who have the certification of the appropriate Board. We will grant immediately that there are others involved in all fields of American specialties, but for demographic enumeration and future prediction, we should confine ourselves strictly to Board-certified personnel, not only because it is the only accurate and reliable number, but because it is the only appropriate approach to future credentialling for specialty work. The American specialty Boards will come inevitably to occupy the key position in specialty credentialling. I am happy to report that we are in correspondence with the 10 surgical Boards and 6 additional Boards in closely related fields, and that they are supplying us annually with their Board Certification rates.

We have been embarrassed to find that it is extremely difficult to determine how many Board Certified surgeons there are in the United States! The AMA tape data are a bit out of date at times, and the American Medical Association does not readily recognize the need to separate out Board certified personnel. It is clearly the obligation of American Surgery to keep its own census up to date. This can best be done by the Boards themselves. Who else can possibly know as authoritatively, precisely who has been certified? Some of the Boards–Orthopedics for example–have already taken the lead here. They keep an accurate census of their personnel. Each American Surgical Board or other specialty Boards should be encouraged to maintain a simple, updated card file indicating the age, sex, activity status, and location of each of their Diplomates; they may wish to add other data for their own purposes. This will then make it possible for the American Surgical establishment, at any point in time, to provide an authoritative reply to the query as to *exactly* how many surgeons there are in practice in the United States. I am hopeful that at the business meeting tomorrow, a resolution may be passed on this subject.

III. Manpower Goals

Now as to the *Manpower goals* themselves. Using a program for specialists on a population base, developed by our laboratory computer group in surgical research, we are able to make accurate predictions running through for the next 30-50 years.* These predictions depend upon the input rate, the death and retirement rate, and the current age group distribution. The input rate is a function of the Board Certification rate, and this in turn is the *effective* index of the annual output of the total residency program in each field. The death and retirement rates have now been corrected and verified with several of the surgical specialties, and I believe they are very hard numbers. The current age group distribution has been dug out of the "Directory of Medical Specialists" man-by-man, by workers in my laboratory; it has been a tremendous task but now we have the numbers and can proceed from here. We are hopeful that the AMA data bank will provide us further information in an attempt to check out their data against ours.

Manpower goals can be of any type you might prescribe. One could state that he wished to plan a manpower goal which would double the number of surgeons in the next fifty years. Or, one could lay out the numbers for a manpower goal to cut the number of radiotherapists in half. Instead of such drastic plastic surgery on any specialty manpower, we have looked at three types of goals as follows:

a) *Constant input*. This is the manpower goal that would be achieved if exactly the same number of surgeons were certified each year, that are now certified. Because of the age group distributions, this would produce a 25% growth in most of the specialties by 1990.

b) *Constant population ratio*. This is a manpower goal based on the concept that we wish to have no growth in the surgical professions, and that the numbers would remain constant in relation to the population which is growing at the rate of about 0.6% per year. This is a "zero growth" goal, which I believe is impractical.

c) *A flexible modest growth rate goal*. This involves the objective of a 1% growth in population ratio for each of the 10 surgical specialties, each 5 years. That is to say if a specialty had a population ratio of 10.0 surgeons per 100,000 population in 1975, it would move to 10.1 surgeons per 100,000 population in 1980. Because of population growth rate, this involves an absolute increase of numbers of about 1% per year. Tables 1 to 3 are examples of the 22 manpower goals that we have worked out for the various specialties.

Please note that these are expressed both in absolute numbers and in "per cent of current output rate." It is obvious that some of the specialties are going to have a sharp cutback for the next 10 or 15 years, cutting off some of the lower quality residency programs, and tightening up their whole manpower production, to avoid excessive growth of their own field.

In Anesthesiology, Internal Medicine and Pathology, it is our belief that there is a real manpower shortage. We have developed alternative manpower goals for those fields, that involve a 20% growth in population ratio in the next few years (Table 4).

These are the types of manpower goals that we should examine, discuss, and then enforce to our own national

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*This predictive program is available in the Long Form Report.

Year	Cert. Rate	% of past 5 yrs.	Total at close	Spec./Pop.
1972-77	13027 (2605)	100.0	57153	26.89
1977-82	10202 (2040)	78.3	61243	27.16
1982-87	10457 (2091)	80.3	64270	27.43
1987-92	11310 (2262)	86.8	67018	27.70
1992-97	11881 (2376)	90.8	69311	27.98
1997-02	12621 (2524)	96.9	71417	28.26
2002-07	13424 (2685)	103.0	73359	28.54
2007-12	13777 (2755)	105.8	75101	28.83

TABLE 1. *Manpower Goals in the Specialties: All Surgical Specialties.*

voluntary establishment organizations. It is my belief that the CCME or the LCGME (Liaison Committee on Graduate Medical Education) is the ideal organ to undertake this type of self-discipline and manpower constraint.

Most importantly, we need some sort of national agency that will continue to look at these numbers, continue to set and modify goals, and that will be responsive to the needs of surgeons and of patients to have realistic manpower goals.

We should recognize again that for each surgeon it comes as a bit of a shock to think that reproduction of his own kind might be held under some sort of reasonable birth control. Better to have birth control, that is to say, control of the total residency programs, than abortion. It is certainly unwise to try to control this mechanism by cutting off the trainee after he has already had 4-6 years of gestation in a very poor program, requiring forcible removal from the system by flunking the exam. Furthermore, we have learned that there are many survivors to this process, and it does not help American surgery at all.

This, then, seems to be the message about manpower goals that comes from our committee work. It is most particularly a continuing obligation and a fascinating problem that must be looked at repeatedly, and annually. This is one of the main jobs of the Committee on Issues.

IV. Misuse and Misinterpretation of SOSSUS Data

Lastly, I would like to close by saying a few words about ways in which I believe the SOSSUS data will probably be misused and misquoted.

In the first place, 60% of all the 18 million operations in the United States can be described under 50 names; by far the most common is obstetrical delivery; the next commonest include fracture reduction and tonsillectomy. We are therefore going to feel pressure to *train two kinds of surgeons*, a sort of "two track theory," under the disguise of public economy. We will be asked to train a "routine surgeon" and then another surgeon who can do the fancy things. The simple surgeons will do those 50 operations and then someone else will do the other more complicated procedures!

Incidently, some of the 50 very common procedures are not things that you would like to have carried out on members of your family by someone who was a technician rather than a physician.

The two track system of training is absolutely unacceptable. It would place the majority of surgery in this country in the hands of those least qualified. Who could possibly do the policing to see that other operations were not carried out by these people? This is a very large

Year	Cert. Rate	% of past 5 yrs.	Total at close	Spec./Pop.
1972-77	2920 (584)	100.0	15635	7.22
1977-82	2470 (494)	84.6	16444	7.29
1982-87	2989 (598)	102.4	17256	7.37
1987-92	3329 (666)	114.0	17994	7.44
1992-97	3435 (687)	117.6	18610	7.51
1997-02	3373 (675)	115.5	19176	7.59
2002-07	3323 (665)	113.8	19697	7.67
2007-12	3409 (682)	116.7	20165	7.74

TABLE 2. *Manpower Goals in the Specialties: General Surgery*

TABLE 3. *Manpower Goals in the Specialties: Urology*

Year	Cert. Rate	% of past 5 yrs.	Total at close	Spec./Pop.
1972-77	932 (186)	100.0	3953	1.82
1977-82	675 (135)	72.4	4157	1.84
1982-87	763 (153)	81.9	4362	1.86
1987-92	813 (163)	87.2	4548	1.88
1992-97	845 (169)	90.7	4704	1.90
1997-02	903 (181)	96.9	4847	1.92
2002-07	973 (195)	104.4	4979	1.94
2007-12	971 (194)	104.2	5097	1.96

country and operations that are considered as "rare" are those that have a statistical incidence of less than 0.5 per thousand population per year. This actually means 100,000 such operations per year in the U.S.! It includes *all* of the operations in the various cancer fields and well as vascular and cardiac surgery. The total operative rate in the United States is almost 80 operations per 1000 population per year. Some of the rare ones are tough and demanding.

To reduce one category of so-called "surgeons" to those who simply do repetitive operations over and over again without careful consideration of the patient and of other alternatives, would be to set the clock of surgery back a hundred years.

Second, because of the relatively light operative workloads reported by most American surgeons, there is going to be pressure to have the *number of operations performed per year become a criterion for continuing re-certification*. It is true that there is a point there that does need further study and definition; what are the operations wherein a critical mass is required for maintenance of skill? This is one of the matters being looked at by the Committee on Issues.

TABLE 4. *Alternative Manpower Goals in Pathology, Anesthesiology and Internal Medicine: Goals Based on a 20% Increase in Population Ratio by 1992.*

Year	Increase in Spec/Pop Ratio	Certification Rate 5-Yr	1-Yr	% of Start	At Close of 5-Yr Period Total	Spec/Pop
		I - PATHOLOGY				
1972-77	0%	2003	(401)	100.0	8878	4.10
1977-82	10%	2061	(412)	102.9	10170	4.51
1982-87	6%	2036	(407)	101.6	11201	4.78
1987-92	4%	2102	(420)	104.9	12025	4.97
1992-97	1%	1992	(398)	99.4	12434	5.02
1997-02	1%	2202	(440)	109.9	12812	5.07
		II - ANESTHESIOLOGY				
1970-75	0%	1291	(258)	100.0	5572	2.57
1975-80	10%	1161	(232)	89.9	6277	2.83
1980-85	6%	1300	(260)	100.7	6927	3.00
1985-90	4%	1370	(274)	106.1	7460	3.12
1990-95	1%	1370	(274)	106.1	7739	3.15
1995-00	1%	1503	(301)	116.4	7992	3.18
		III - INTERNAL MEDICINE				
1970-75	0%	4332	(866)	100.0	20717	9.56
1975-80	10%	4708	(942)	108.7	23324	10.52
1980-85	6%	5031	(1006)	116.1	25745	11.15
1985-90	4%	5028	(1006)	116.1	27736	11.60
1990-95	1%	4604	(921)	106.3	28784	11.72
1995-00	1%	4812	(962)	111.1	29717	11.83

Note: The above three fields have been selected as three in which manpower growth should be encouraged at a rate far greater than 1% per 5 year increase in population ratio. An alternative goal, based on a 20% increase by 1992, in the population ratio, is therefore shown.

Although surgical workloads may appear low, some control over the total numbers doing surgery should raise workloads, as indicated below. More importantly, were one to make the annual operative record of a surgeon–in sheer numbers—a criterion of his fitness, it would constitute a tremendous impetus to the performance of operations without regard to necessity.

Actually, the lowest operative workloads are at two ends of the career pattern, people starting practice and those closing practice. Those in multi-specialty groups usually start out with higher operative workloads than those starting in solo practice. I believe all the evidence at hand points away from the advisability of using operative workloads as a criterion of re-certification. It is more important to look at the operative "mix" of the surgeon. The operative record of the prior year should be made available to the Joint Commission on Accreditation and it should not in any way be equated with a "laundry list" of permitted procedures, an ineffective step at best.

A very real problem pointed up by the SOSSUS report has to do with the *fate of residency training programs in the specialties*, wherein 50-70% of the residents currently are foreign medical graduates. This applies to three fields that are very close to surgery, namely radiology, anesthesia, and pathology. If foreign medical graduates were rapidly phased out, those fields would find a burden in delivering their service load, that could be embarrassing to the performance of adequate surgical care. The Committee on Issues is looking into that matter in greater detail. I think we should fight off the concept that "physicians assistants" can provide a one-to-one substitution for interns and residents. It would be far better to reorganize the staff so the junior staff members assist with coverage at a proper reimbursal level, with the help of physician's assistants when appropriate.

We are going to be under pressure to *redistribute physicians by redistributing residencies*. This is the so-called "parochial" approach to residency distribution. I am not sure that plan will ever work. An adequate residency depends upon the educational validity of the hospital, and not its location in a so-called underserved area. For surgery the main issue is to define the underserved and undersupplied areas. The data from the SOSSUS Manpower Study are very complete indeed on this point. We cannot identify any areas of the country that are seriously undersupplied by Board-certified surgeons; there are uneven distributions of ancillary professional personnel, particularly in anesthesia and pathology. I know of no evidence that relocating residencies in hospitals that do not now have them because of lack of educational facilities, will in any way ameliorate this problem. Some of the underserved areas are large city ghettoes. In these very centers of underprivileged population there are some of the largest teaching hospitals in the country; in other instances the underserved area is literally ringed around by hospitals known throughout the world for their superb residency training programs. Clearly, the matter is one of *access* to the medical care system by the patient. Putting a large teaching hospital out in the middle of the country where there are relatively few doctors, will likewise be an absurd expenditure of the taxpayers' money. Better to improve the triage and mobile referral system, rather than to embark on the forced redistribution of residents.

I will not comment on the concept of enforced or indentured service to populate so-called underserved areas. A two-year stint in a rural community is not going to produce the sort of small group practice that would really improve care in that region.

Finally we are going to see some *unrealistic manpower goals* pushed in the direction of surgery, and based on the annual operative workloads of surgeons in Sweden and Great Britain. The physician mix in both those countries lends itself to higher workloads by surgeons because the general practitioner is recognized as the appropriate source of referral; the surgeon is not saddled with nearly as much primary care, triage and followup as he is in this country. It is very unlikely that surgeons in this country could suddenly achieve the high annual workloads reported from Sweden and Great Britain, unless there were a global re-alignment of medical care in the country as a whole. If the 30,000 persons who now carry out surgery but without Board Certification were to stop doing that surgery over a 7-10 year period, it would increase surgical workloads amongst the Board Certified group and their residents, from about 200 to 230 operations per year. This would seem acceptable. The income increase would be modest, about 10% in lifetime income.

And yet, we are going to see our request for a modest reduction in surgical residency programs greeted as a bid for higher incomes on the part of surgeons. We have already seen this misinterpretation in the hands of one journalist. In point of fact, our desire to constrain some residency programs and encourage others is a response to societal pressures to redistribute medical care in this country and to improve primary care. Nothing will make surgery more efficient, more rapidly, than an improvement in primary care and access modes.

Critics of surgery cannot have it both ways! If they perceive that there are too many surgeons in this country and the surgical establishment agrees to a modest reduction in surgical residency output, then it is totally inappropriate for those same persons to accuse American surgery of financial self-interest in a modest increase in operative workloads.

Within two months, the Summary Report of the SOSSUS Study will be in the hands of each member of this Association. I hope each person will read it carefully. Speaking for our own Manpower Committee, I can say that we invite questions, comments, criticisms, and above all, we invite the opportunity to present these data to medical or political groups and legislative committees who could stay closer to reality on the basis of the SOSSUS Study.

Again with many thanks to President Muller, Dr. Zuidema and his staff, the work of the Manpower Committee is closed out and the work of the Committee on Issues has begun!

SOSSUS and the Outlook for American Surgery

GEORGE D. ZUIDEMA, M.D.

THIS MEETING marks the conclusion of SOSSUS,* a study which has consumed our interest for the past five years, and which has the potential to influence our professional lives for at least the next two decades. As your Chairman, I would like to present this final report to the Association.

From the standpoint of SOSSUS operations, we will complete our work on June 30, 1975. Our work has had the unprecedented support of the profession, and many of you have made important contributions to our study. Our summary report will be published in June, and will be made available to all Fellows. A much longer, detailed report will be published by the Government Printing Office later this year. This material, containing the data upon which the summary volume is based, will be available to libraries and serious scholars interested in the field.

The total financial commitment to the study totaled \$1,473,927. This includes \$141,592, contributed by the American College of Surgeons, The American Surgical Association, the participating Surgical Specialty Societies, and the Four Regional Surgical Societies. The sum of \$160,500 was contributed by the Robert Wood Johnson Foundation, Commonwealth Fund, The Henry J. Kaiser Family Foundation, Richard King Mellon Charitable Trusts, Rockefeller Foundation, Matilda R. Wilson Fund, and the Walnut Medical Charitable Trust. Federal grants and contracts in the amount of \$721,835 were obtained from the National Institutes of Health (Bureau of Health Manpower Education, and the National Institute of General Medical Sciences), the Health Services & Mental Health Administration, and Health Resources Administration (Bureau of Health Resources and Development).

My second, and most important objective is to take this final opportunity to identify certain major problem areas which have emerged from the study, and present my own personal ideas on these subjects and how they might be approached. It is virtually impossible, in such a report, to cover the entire scope of the study. This report will be limited to a relatively few specific areas which appear to be of most immediate importance and which are likely to require our prompt attention. I would like to emphasize the personal aspect of these reflections, for they in no way reflect policies or conclusions decided upon by either the SOSSUS Executive Committee or our sponsoring professional bodies—The American Surgical Association and the American College of Surgeons.

The problem which has emerged as our most pressing issue is that of professional liability. This has reached crisis proportions in several states at the present time and will demand our most urgent attention. This subject will be covered by Dr. Schwartz in the following pages. My deferral, however, should not be interpreted as complacency, for our ability to carry on effectively with our clinical work is absolutely dependent upon finding a rational solution to this dilemma.

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*Study on Surgical Services for the United States.

Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

TABLE 1. *Estimates of Total Surgical Manpower*

I		
Board certified specialists	48,813	
Less dual boards	2,351	
	46,462	
Non-board certified surgeons	20,621	
General practitioner surgeons	15,821	
Interns and residents	9,708	
	92,612	
II		
Totals—excluding interns and residents		
Board certified surgeons	46,462	60.50%
Non-certified and gp surgeons	30,329	39.50%
	76,791	

The second area which has commanded national attention is the entire broad subject of surgical manpower and workloads. Here the landmark studies of Dr. Moore's committee have provided the basis for both an understanding of the dimensions of the problem, and some possible solutions. The Congress and the lay press have concluded that there are now "too many surgeons", and have in many instances attempted to link this to the performance of unnecessary surgery. These conclusions have already led to the de-emphasis of surgery and surgical training which extends to include research and research training. We are beginning to see legislative proposals designed to curtail the output of surgical residents. The "overkill" which might result from such steps could be anticipated to have significant deleterious effects on surgical care.

This audience is, of course, familiar with the manpower figures which suggest that the heart of the problem lies in too many people performing surgery. Fully one-third of the total surgical manpower pool is made up of non-certified surgeons and general practitioner surgeons (Table I). This group performs a significant proportion of surgical work, as shown by Dr. Moore's area studies where from 39 to 51% of physicians performing operations in 1970 in those specific regions were either non-board certified surgeons or general practitioners (excluding interns and residents), and these groups performed 32 to 42% of the total number of operations (Tables 2 and 3).

The matter of surgical workload is also of interest. Hughes, et al. studied 19 general surgeons in community practice in the New York metropolitan area and found their median weekly operative workload to be 3.1 hernia equivalents.[1] A later time-motion study showed their mean observed six day work week to be 34.5 hours, of which 28.7 hours were devoted to professional activities.[2] The Hughes studies based on the work of 19 surgeons are widely quoted and used to illustrate "underutilization" of surgical manpower. These authors have made comparisons with surgeons practicing within a prepaid group where each surgeon performs roughly three times as many operations. It is difficult to conduct a time-motion study of one group and conclude that the participants are "underutilized"without having identical studies of other professional groups for comparison. Furthermore, professional responsibilities include much more than operating room performance, and these differences must be borne in mind in comparing total surgical practice. We also know that some surgeons are busier amd more capable than others and we must be aware of putting too much emphasis on averages. Surgical work will never be spread out to "average surgeons".

We know that there are wide variations from one type of practice to another, depending on whether one is dealing with University surgeons, solo or multiple specialty group practice, prepaid programs, and whether or not they are Board certified. Operative workload is known to vary from one section of the country to another, depending not only on surgical manpower, but upon the mix of access and service physicians available in the area and how much primary care is offered by the practicing surgeons.

For comparative purposes, we can look to the Moore-Paterson area studies and convert their annualized figures to weekly operative workload and hernia equivalents (Table 4). The variation in workload from region to region seems to average out somewhat, and it is clear that the non-certified surgeons are in general performing

TABLE 2. *Primary Specialty of Physicians Performing One or More Operations in 1970**

	Area A	Area B	Area C	Area D
Primary specialty:				
Board certified	30.0	36.3	24.0	33.7
Not certified	21.8	15.5	16.1	14.4
Medical specialists	27.2	15.5	24.5	18.4
General practitioners	16.9	32.7	35.0	27.3
Osteopathic surgeon	3.5	0	0.3	5.0
Osteopathic physician	0.6	0	0.2	1.1
	100.0	100.0	100.1	99.9

*Excludes interns and residents.

TABLE 3. *Per Cent of Total Operations Performed by Primary Specialty of Physicians*

	Area A	Area B	Area C	Area D
Surgical specialists:				
Board certified	53.0	50.6	49.7	53.4
Not certified	30.3	15.3	24.3	17.8
Medical specialists	2.1	0.6	2.4	1.6
General practitioners	4.1	13.2	17.1	14.3
Osteopathic surgeon	2.9	0.0	0.0	2.7
Osteopathic physician	0.1	0.0	0.0	0.3
Intern or resident	7.0	20.0	4.8	9.9
Unknown	0.4	0.3	1.7	0.2
	99.9	100.0	100.0	100.2

fewer, and less complicated operations. An important consideration here is to what degree it is reasonable to expect *total* workload to change and what, in terms of hernia equivalents or any other standard, the ideal should be. The factors must be discussed in depth before conclusions regarding the "ideal" surgical manpower pool can be reached.

There are many other variables to consider, but these are mentioned only to highlight the difficulties which are encountered when conclusions are reached from statistics which are either too simple or too general in nature and then translated to a national scale. Congress has shown signs of taking action without studying the full impact of some of the legislative proposals. It will be necessary for the profession to assist in the development of new manpower patterns, calling upon our well established statistical base and our knowledge of the intricacies of planning for patient care.

The manpower aspect can be resolved into two specific problems. First, the establishment of effective credentialing, which can define and enforce who should be performing surgery. Secondly, the adjustment of residency positions to train appropriate numbers of surgical specialists. While neither of these problems is easily solved they could be approached, however, by initiating a series of steps.

The problem of credentialing will require several changes, aimed at both control of the current situation and limiting the future pool of non-certified and general practitioner surgeons. An immediate ruling, whether by law or by insurance regulation, which would limit payment to a group of certified surgeons would probably be undesirable and produce serious side effects in many areas where good surgical care is now offered. It would be difficult to estimate the full impact of such an abrupt change, and it is my belief that a deliberate transition would be preferable. How then might this be accomplished?

There are 5,770 short-term non-Federal hospitals in this country, where some 50,000 operations are performed each day. All of these hospitals are state licensed, but only 4,236 are accredited by the Joint Commission of Accreditation of Hospitals, and 128 more are accredited by osteopathic authorities. The first step might be a Federal or State requirement that all hospitals be properly accredited by either the JCAH or its osteopathic counterpart. This would at least ensure fairly uniform standards throughout the country. The JCAH, through its efforts on Quality Assurance and delineation of staff privileges, with backing from patient care statistics derived from PSRO, would be in a position to enforce departmental review of physician performance in maintaining quality of care.

The second step should be one designed to curtail the expansion of the group of non-certified surgeons entering practice. While one may argue that Board certification may not be the only criterion for excellence, the fact remains that the boards have established reasonable educational requirements and an examination process aimed at identifying surgeons qualified to be responsible for the

TABLE 4. *General Surgical Weekly Workload**

	Area A	Area B	Area C	Area D
I Board certified				
Average # operations	3.5	3.9	4.1	3.1
CRV Adjusted	38.5	39.0	41.0	37.2
Hernia equivalents	4.3	4.3	4.6	4.1
II Non-certified				
Average # operations	2.3	2.1	2.9	1.98
CRV Adjusted	23.0	18.9	26.1	17.8
Hernia equivalents	2.6	2.1	2.9	2.0

*Based on Moore-Peterson area studies.

TABLE 5A. *Per Cent Failures, American Board of Surgery: Part I-Examination*

	First Examination			Re-examination			Total
	Domestic	Foreign	Total	Domestic	Foreign	Total	All Candidates
1970	12.6%	46.2%	24.8%	57%	65%	62%	33%
1971	13.8	53.4	30.1	57	76	70	41
1972	14.0	55.2	29.9	55	73	68	41
1973	14.4	49.0	28.0	65	70	69	41
1974	14.4	50.4	29.4	67	80	76	45

surgical care of patients. The board certificate has become accepted as a standard, indicative of professional quality control.

Unfortunately, there are two problems related to the use of the board certificate as the primary credential. As we know, failure to achieve board certification has not limited anyone's ability to practice surgery, provided that he can obtain hospital privileges. Secondly, we are all familiar with the high failure rates for the American Board of Surgery examinations (Table 5). Diplomates and failures alike go out to practice surgery, and the size of the pool of uncertified surgeons will continue to expand unless steps are taken to control this at the source. The high failure rare is a cause for concern, because it indicates either inadequate professional background, or poor educational settings for the unsuccessful candidates. The tragedy, of course, is that these unsuccessful candidates have spent at least four years in obtaining surgical training, only to fail the certifying examination. In a situation where only those with proper credentials are permitted to practice surgery, they would have no professional alternatives open to them. The solution to this problem could be found in the establishment of a mandatory qualifying examination. Successful passage of which is required of *all* surgical residents *prior* to entering the latter years of their general surgical or specialty training. This could function as an effective screening mechanism, so that the Part I and Part II exams would not have to serve this purpose, and consequently, the failure rate could be expected to drop. At present the Boards of Orthopedics, Ophthalmology, Anesthesiology, Otolarynogology, Neurosurgery, Plastic Surgery, and OBGYN offer in-service examinations. The American Board of Surgery will offer its first in-service examination in September, 1975. All but the Orthopedics and Neurosurgery examinations are voluntary, however. Although voluntary evaluation is of help in demonstrating areas of weakness to residents and program directors, this examination cannot fulfill a screening function unless it becomes mandatory, with successful completion required before *acceptance* for further training. Although the addition of another hurdle may be looked upon with disfavor, it is far superior to the investment of four or more years of training, with the significant possibility of failure at the end.

The next assignment facing us is the adjustment of residency positions to provide for the continuing output of surgical specialists in numbers appropriate to meet our national needs. At present, of course, there is no real restriction on numbers of training positions. These are limited only by whether or not specific programs can receive approval by the Residency Review Committee with review by the Conference Committee on Graduate Medical Education. There are approximately 16,000 surgical residency positions offered in this country today, with about 12,000 surgical residents in training. Four thousand positions are vacant each year. During the period 1968-1972 an average of 2,600 individuals completed residencies each year and achieved the preliminary credentials necessary for Board Examinations. Based on precise manpower data which can be adjusted for such other factors as rate of population growth and death and retirement rates, it is possible to predict the ratios of surgical specialists per 100,000 population over the next 25 years. Dr. Moore's data would predict an increase from 23 per 100,000 in 1971 to 27 per 100,000 in 1996, if we continue to train individuals *at current rates*. This is an increase of more than 17%.

All of our information therefore, would seem to indicate a need to cut back in the number of residency positions offered. A major problem facing the profession is how this can be accomplished on a voluntary basis short of the legislative establishment of a quota system. We have already seen proposals to allocate approximately 50% of all training positions to those designed to prepare physicians for primary care. The *total* number of training positions to be offered in *all* medical disciplines is at present undetermined because of the influx of Foreign Medical Graduates (FMG) and various efforts by legislative means to restrict the numbers in this category. During the past year, the number of FMG's licensed to practice in this country was nearly the same as the number of graduates of U.S. and Canadian medical schools. The "numbers game" will be exceedingly complex, and full discussion of all of the ramifications is beyond the scope of this report. It is obvious, however, that there will have to be some curtailment in the number of training positions available for the surgical disciplines, and some comments regarding certain basic principles in arriving at these decisions, and how the decisions might be implemented are certainly germane.

TABLE 5B. *Per Cent Failures, American Board of Surgery: Part II-Examination (Oral)*

	First Examination			Re-examination			Total
	Domestic	Foreign	Total	Domestic	Foreign	Total	All Candidates
1970	17.6%	37.9%	23.6%	33%	51%	40%	27%
1971	12.6	32.7	18.4	34	52	41	22
1972	15.6	37.1	22.1	35	54	44	27
1973	15.3	45.4	24.4	34	44	39	27
1974	16.4	45.7	26.3	37	50	45	30

The following considerations are of great importance in achieving a reasonable transition to professional self-regulation of surgical training positions:

1) The surgical specialties will have to meet and agree upon some formula or quota system based upon the annual production of a total of approximately 2,000 surgical specialists. A transition phase will be required beginning with the curtailment of first-year positions available, and proceeding over the subsequent five or six years until individuals now in training will have had an opportunity to complete their residencies. This will require an extraordinary spirit of cooperation and policy should be established and implemented through the voluntary accrediting agencies now in operation, the Coordinating Council on Medical Education and Liaison Committee on Graduate Medical Education. The alternatives are very unattractive.

2) The establishment of mandatory, qualifying inservice examinations in all surgical specialties would help by limiting the individuals in training to those best qualified, and upgrade the quality of those performing surgery specialties.

3) Decisions regarding which programs will be preserved should be based primarily upon the quality of the educational programs, with less emphasis being placed on such other factors as geographical distribution or local political pressures. Information regarding performance of residents on board examinations as is now being made available, will be of help in this kind of evaluation necessary in phasing out inadequate programs. Other factors, such as educational environment, research productivity, and ability to offer well-rounded training are some other factors worth considering. We must not lose sight of the concept of a continuum in medical education, with graduate training taking place whenever possible, concurrently with the education of medical students. Surgical residents play important teaching roles for undergraduate medical students, and this interaction reinforces their own education as well. This, of course, means that the major portion of graduate education will probably be concentrated in or near medical centers.

4) A system for continuing annual data collection will be required, if the production of surgical specialists is to be flexible and adjustable to meet national needs which may change in time. It would be foolish to lock into a system based on present projections, and find that it is impossible to adapt at a later time as our patterns of health care change.

5) It is important to begin to measure the impact of loss of training programs on the hospital-based practice of surgery. New ways will have to be found to meet many of the service functions which are now performed by surgical interns and residents. Whether these services will be performed in the future by surgeon's assistants or by certified surgeons working in somewhat different roles, the surgeons workload will obviously be changed. Information regarding these effects should be fed back into the manpower computer, for a reassessment of the number of surgical trainees that may be required. It is too early to make a firm prediction on data currently available to us.

6) We urgently need a rational solution to the numbers of FMG's which will be admitted to our training programs. This too is a complex issue, but it has obvious significance to several disciplines, such as thoracic surgery, general surgery, pathology, and anesthesiology where the FMG's entering training range from 30% to more than 50% of the total trainees. If FMG entrance into the system is cut abruptly to approximately 25% of the number of U.S. graduates, as has been proposed, the effect is totally unpredictable. It is more logical that such a limitation be achieved over a period of four or five years to allow for a smooth transition to a new steady state of specialist production. It may be that by regulating the quality of approved programs, this issue for surgery may solve itself.

7) The output of surgical specialists must be examined in terms of the geographical distribution which now exists. In our free-enterprise system we have depended largely on chance and personal preference in identifying locations for practice. With a cut of approximately 23% in the output of qualified surgeons, the maldistribution which now pertains may be aggravated further. It will be tempting to use geography as a primary criterion in determining which residencies will survive. To adopt this policy, without due regard to quality, however, would be most unwise and might well result in deterioration of the standards of surgical care. It would make better sense to initiate studies into alternative ways to delivering total medical care. This could include, as but one example, setting up practice groups to serve regional areas, with

upgraded transportation systems being provided to bring the patient to an environment where care of high quality can be provided.

8) The need to restrict the number of training positions in the surgical specialties will also require a careful assessment of the trend to develop superspecialists. We have witnessed an increasing tendency to request the establishment of "Certificates of Special Competence" in highly specialized fields. This subject is highly complex, for there are obvious implications in the area of professional liability and in the potential fragmentation of training programs; not to mention the implications in the regionalization of care by disease category, and the effects which might be felt in the cost of health care delivery as hospitals compete to upgrade their status to compete with each other by offering "full professional services." There are great professional pressures to recognize superspecialties, and in instances where established surgical boards are exercising restraint, professional societies which to step into the training field and produce their own certificates. Such steps would, of course, undermine the role of the surgical boards and bypass the evaluation systems which have been developed and have proven so effective. Fortunately, this entire subject is under continuing study by the American Board of Surgery. The issue is, however, both complex and potentially inflammatory. We, as surgeons, have to deal with a relatively limited number of proposals at the present time. Each small decision has large implications, however, and it is important to keep this within the framework of our existing accrediting agencies.

9) Our information on surgical workloads and the SOSSUS manpower data are based on our current method of delivering surgical care, representing a pluralistic system characterized by multiple patterns. As we all know, there is considerable interest in the development of some national system for health care, although its exact configuration remains undetermined at this time. The movement toward change is, however, real and must be recognized by the profession in adjusting its manpower output. As things now stand, we have little information regarding unmet surgical need, or the demand for surgical services which might materialize under different systems of health care delivery. Any system devised for regulating the production of surgical manpower must have the flexibility necessary to adapt promptly to change. Such studies might be undertaken by the Committee on Issues.

10) The last, but by no means least, factor to be considered in the development of plans to restrict the output of surgical manpower has to do with the plight of academic surgical manpower and the training of surgical investigators. Dr. Zeppa and Dr. Orloff have shown us the increasing responsibilities being shouldered by shrinking surgical faculties. There is strong evidence that the Congress and National Institutes of Health have missed an important point, and assumed that since there are "too many surgeons," surgical research and research training should also be cut back or placed under severe restrictions. The long range implications of such myopic attitudes must be emphasized, if we are to avoid freezing the level of surgical care at approximately its present level for the next decade. After all, surgical teachers are needed to educate *all* undergraduate medical students, and we must continue to train surgical investigators and supply adequate support for their work if we wish to maintain the proud level of performance defined so clearly in Dr. Orloff's report. Failure to make our case will likely result in further deterioration of the academic programs which have been developed so highly over the past 25 years. Although research and research training are under study by the NAS and the newly formed President's Commission, the needs here are urgent.

There is almost an endless supply of topics which might be discussed today, and we have touched on only a relatively few of the issues which requires our urgent attention. My final brief commentary will deal with the problems related to the assessment of the quality of surgical care. Both the ACS and the ASA have a long history of interest and participation in setting high standards for surgical care. The SOSSUS effort in quality assessment suffered from a late start and was hesitantly received by a profession concerned with the problems of liability and beset by PSRO and utilization review. The limited results available to us from the Critical Incident Study, however, show considerable promise. If at all possible, we should find some way of continuing our work in this area. The assessment of the quality of care is an important matter for all of us, and should prove to be a significant educational tool as well. The Critical Incident Study is care oriented, rather than directed at cost containment, and as such has great potential usefulness. This study stands as an important item of unfinished business.

Conclusion

At this point, I would like to express my appreciation to the many individuals who have worked long hours and given unselfishly of their time to see SOSSUS through to this successful conclusion. This includes a special note of thanks to our Executive and Advisory Committees, to Mr. George Sideris, and our committee chairmen. It also extends to the approximately 140 individuals who have worked as committee members and consultants, and to the American Surgical Association Councils and Regents of the American College of Surgeons during the past five years. Without the unswerving support of all of these individuals, this task would have been infinitely more difficulty.

This then is a report of my stewardship as your chairman. I would be remiss, however, to close the book on SOSSUS without pointing out that in reality it is but a beginning. We have collected an impressive set of data on virtually all aspects of surgical care in this country. I am sure that all of us who have been committed to this study now wish to see it used to bring about needed improvements in care. The reincarnated Committee on Issues will be one instrument by which this can be accomplished. There are other needs, however, which will require the assistance and cooperation of all medical and surgical specialties. These include: 1) the development of some effective voice which can work with government for constructive change while avoiding the serious pitfall of developing legislative patterns in absence of professional input; 2) a second requirement is the commitment and resources to maintain data collection in critical areas such as manpower, research, quality of surgical care, and the delivery of surgical services. A significant base has been established but it must be updated annually at least if we are to deal with constant change to meet national needs. The assistance of all surgical boards will be required in this work.

It has been both an honor and a pleasure to be able to work in this important area. This is my opportunity to thank the Fellowship for their support and encouragement over the past five years. The SOSSUS summary report will soon be in your hands. I hope it will serve to broaden our horizons and open the way for our continuing work toward maintaining the high quality of surgical care in the United States.

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SOSSUS Legal and Ethics Committee:*

Summary Report on Professional Liability

HENRY G. SCHWARTZ, M.D.

IN HIS ELOQUENT CALL to arms yesterday, President Muller presented some of the problems with which the SOSSUS committee has been contending. This morning, Dr. Zuidema, the guiding light of SOSSUS, has outlined the areas of importance which have been surveyed and which demand continued attention in the future. Thus, redundancy will inescapably color my presentation.

There is a growing force of well informed consumers who prefer a role in determining health policies. From the public point of view, the quality of health care is assessed through the outcome of the services rendered rather than through the provider and practitioner credentialing process. This implies corrective action if care does not meet acceptable criteria and reassessment of such action.

That we are not entirely alone in our suspect position in an increasingly litigious era is exemplified by an article which appeared in the St. Louis Post-Dispatch two weeks ago and which has a somewhat familiar ring: "When Peter Doe graduated from a San Francisco public high school in 1972, he had report cards that indicated he was an average student . . . His attendance had been satisfactory and his mother was a college graduate who had demonstrated repeatedly an interest in his educational progress. He had just one problem. He was practically illiterate. Reading a job application was beyond him . . . Tests showed that after twelve years of school he was reading and writing at the level of a fifth grader. So he sued the San Francisco School district for $500,000 . . .

Among those potentially liable for malpractice suits today are doctors, lawyers, architects, engineers and accountants. But until the Doe case, no one apparently had thought to sue teachers for failing to teach or—more precisely—to teach in the manner expected of a reasonable, prudent professional. The Doe case would appear to be the ideal opportunity to break this new ground. 'Negligent' is the key word in the brief which (the lawyer) filed . . . The damage that resulted from this negligence, the brief contends, ranged from Doe's suffering mental distress to a loss of earning capacity. Ergo, the request for $500,000. The case is awaiting consideration in the California Court of Appeals."

By Mellinkoff's definition in a 1970 article in PHAROS, "the Satanic axiom is that for any problem, however complicated, it is possible to identify one devil responsible for all the trouble." As a corollary, "the more complicated the problem the more time is saved by exercising the axiom." With some justice we have directed our main arrows against some members of the legal profession, but it is questionable whether sufficient pressure can be brought to bear directly that would lead them to alter their adversarial tractics.

Without going into the details of the full report of our committee, I would like to summarize quickly the recommendations which have been made with regard to professional liability:

1) There is a continuing need for informational data to reflect change in the legal environment, and the causes, cost and stimuli for claims.

2) Legislation is needed to require and enable state medical boards to document and report the results of settlements and judgments. With such information the boards would be in a position to correct problems of substandard care and promulgate remedial education measures.

3) Additional legislation which requires the presentation of these data to state insurance departments for the development of sound actuarial and rate-making insurance procedures should reduce health care costs.

4) Legislation should be enacted giving state medical

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*Study on Surgical Services for the United States.

Presented at the Annual Meeting of the American Surgical Association, Quebec City, Quebec, May 7-9, 1975.

boards adequate power for disciplining practitioners for incompetence of who manifestly pursue irregular, inappropriate, unnecessary, and improperly applied procedures. Rehabilitation rather than permanent removal from the health care system should be emphasized.

5) Litigation often fails to provide a fair result for all concerned. Broader enactment of statutes would be desirable to: (a) Standardize informed consent; (b) Stabilize the standard of care; (c) Restrict the use of res ipsa loquitur; (d) Regulate contingency fees; (e) Establish reasonable limitations of amount of judgments.

6) Pre-trial screening panel systems as codified in New York and New Hampshire, and binding arbitration would be favorable substitutes for the jury system if it can be shown that these are effective methods in reducing the costs and delays of litigation.

7) Prevention programs should be intensified to minimize the risk of injuries. These programs should be the concern of agencies and professional staff committees which monitor and evaluate the quality of health care to provide effective peer responses to adverse incidents to patients.

8) There is an increasing need for courses in continuing education in medicine and preventive education measures in legal medicine. (This has been repeatedly emphasized by the AVS Governors Committee on Professional Liability.)

9) There is a need to educate all patients concerning hazards, risks, costs and limitations of medicine to reduce disappointment or dissatisfaction with the outcome of treatment.

10) To make the public aware of the cost of insurance which hospitals and physicians have to pay, it may be desirable to include an explanatory statement in the patient's bill; or to have the patient pay the malpractice premium through Blue Cross, Blue Shield or other health insurance carrier. Perhaps the government should act as a reinsurance mechanism for malpractice insurors to reflect and absorb the cost of litigation in the social security system.

To preserve the availability of liability insurance coverage, a method must be worked out to protect practitioners against sudden cancellation of policies. There should be contingency plans for coverage in areas or states where insurance becomes unavailable. This could take the form of shared risks through consortiums of carriers.

To control skyrocketing costs, there has been some support for the creation of a no-fault concept in the malpractice field. To be effective and remain within fiscal feasibility, it would be necessary to set exact criteria for determining what would be a compensable medical maladventure, along with appropriate limitations of judgments. Short of this, disability from any illness would have to be compensated at enormous overall cost.

Some physicians have been sued for actions they have taken in good faith as members of hospital review credential committees. Physicians selected to serve on such official bodies should be immune from such suits or be indemnified by the institutions they serve.

11) Changing rules on informed consent, substituting a legal standard to measure the physician's conduct rather than the custom of the medical profession, imposes a burden in imparting information which is frequently impractical and time-consuming, often difficult to articulate and which may produce unnecessary anxiety in patients undergoing surgery.

12) We recommend enactment of a uniform standard of consent for treatment, for disclosure of risks to patients *in accordance with the local custom of the profession in each jurisdiction.*

13) In matters of informed consent, the best legal protection flows from the surgeon obtaining consent himself and documenting this in the patient's record.

In the past few months, problems with professional liability insurance coverage have resulted in a wave of publicity and protest, finally reaching the attention not only of previously concerned federal officials but, more importantly, of occupants of our state legislative houses.

Availability of insurance has been handled in separate ways by state legislatures. As of the date of this presentation, joint underwriting associations have been established requiring insurors doing business in California, Idaho, Wisconsin, Indiana and Arkansas to write malpractice insurance. In North Dakota, Maryland and Missouri, an alternative method of availability, a Physicians' Mutual Company, has been established through state legislation. It may be expected that other legislatures would rapidly enact statutes providing availability before the close of the current sessions.

One additional development, the state fund concept, has been enacted in Indiana. This provides an insurance pool for amounts of awards over $100,000 and up to $500,000. This fund is state managed and is accumulated by assessing a 10% charge on each premium written in Indiana. In concept, this amounts to self-reinsurance. Idaho and Indiana have put a ceiling on recoveries at $150,000 and $500,000 respectively. Idaho has also established a New Jersey type limitation on contingent fees. Indiana allows a 15% fee for awards over $100,000. Other housekeeping sections were enacted in both states. Indiana has also established a state mediation board which will decide liability and the amount of permanent impairment. There is a possibility that frequency of claims might increase in Indiana if the board is too liberal.

We may anticipate other omnibus legislation in Florida, Ohio, New York, Illinois and possibly other states. However at this time the above are the current established statutes.

The Blank Subcommittee of the NAIC (National Association of Insurance Commissioners) has adopted a separate line of business for malpractice insurance to be included in the 1975 annual statement for all insurers. It will provide data for each insuror on loss and expense ratios, investment income, taxes and profit. It will also show premiums and losses for each insurer in each state.

The professional liability subcommittee of the NAIC has developed a statistical form for closed claim data for medical malpractice. It calls for certain information to be reported on each claim that is closed after July 1, 1975. The data will provide information regarding the nature of the injury, the claimant, the defendant(s), the settlement, the location and circumstances of the incident, the date of the occurence, reporting and settlement. The data will be coded and maintained at NAIC headquarters in Milwaukee. The closed claim data will be reconciled with financial information and could profitably dovetail with statistical data bases used in health care such as PAS (Professional Activity Survey) in Ann Arbor. The financial impact is obvious. The statistical information will be very useful in loss prevention and risk control when compared with the universe of injuries in hospitals and other facilities. Obviously there is an intent to insure sound rate-making in each state. Since January 1975 the insurance regulators have been actively working on the claims-made policy to guard against sharp insurance practices in the industry. They have also been active in establishing joint underwriting associations and conferring on malpractice legislation in each state.

On the Federal scene, the Senate Subcommittee continues to hold hearings on Bill S215 establishing a Federal no-fault insurance program. Several of the high risk specialties testified at these hearings. Additionally Senator Kennedy has an alternative bill to establish a Federal Arbitration System for Malpractice, and Senator Nelson has introduced a bill for Federal re-insurance.

Congressman Hastings has introduced Bill H.R. 6100, the Medical Malpractice Clains Assistance Act. This bill would create a Federal re-insurance pool to cover awards in excess of $200,000; each state would create a medical injury arbitration board which would be non-binding, except that parties may contract to be bound by arbitration. All awards based upon future losses would be paid out on an annuity basis; a New Jersey sliding scale for contingency fees would be applied; a statute of limitations for all claims would be two years after injury, except that a minor under six years may make a claim at any time before he is eight years old. Providers would contribute to the insurance fund based on their basic insurance premiums, therefore surgeons would pay more; professional risk control programs would be established, together with patient grievance mechanisms; and finally collateral sources would be deducted in the computation of awards.

For the short range stop-gap, preserving the market place for malpractice insurance at a reasonable price will continue to be the most pressing problem. Hopefully, in time, adequate legislative solutions will be found at the state level, to resolve inequities in the legal system. Aware of the nature and mechanisms of legislative change, we shall need the support of all concerned, including the public whom we serve.

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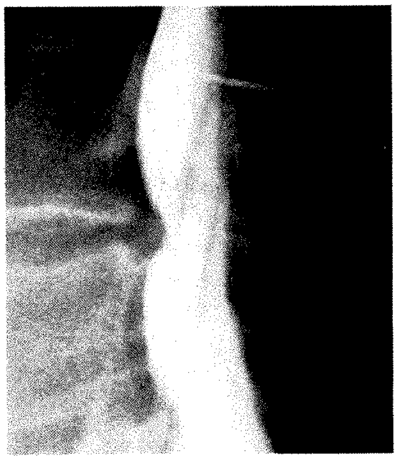

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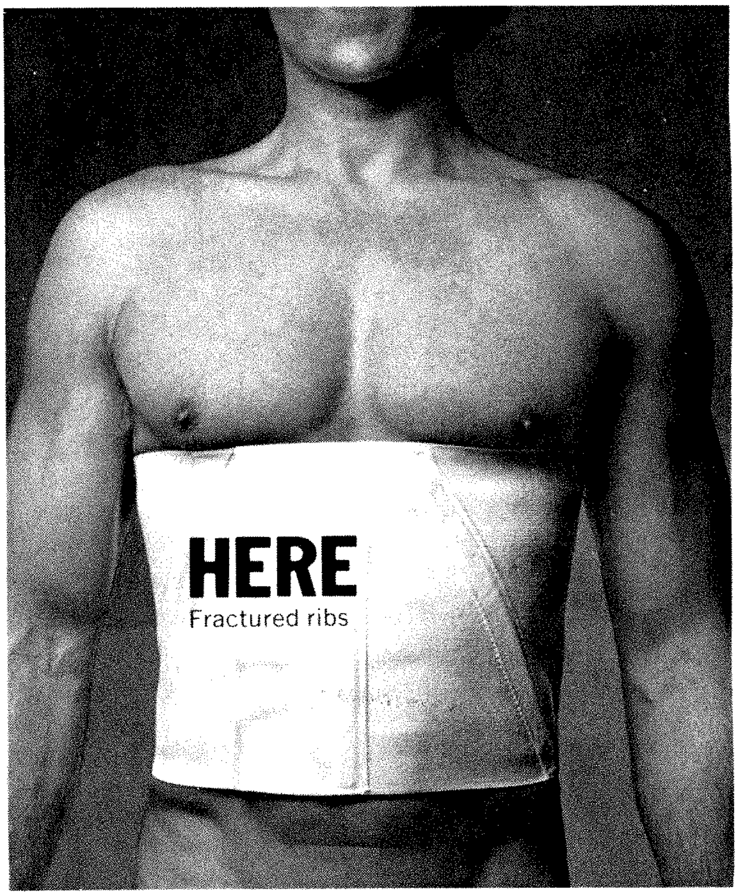

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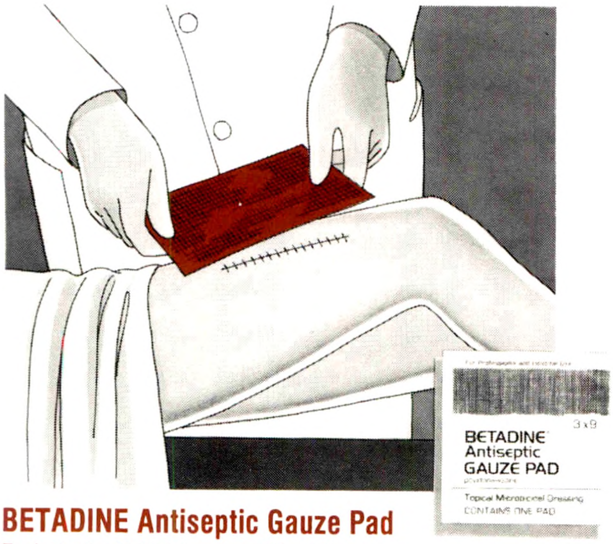

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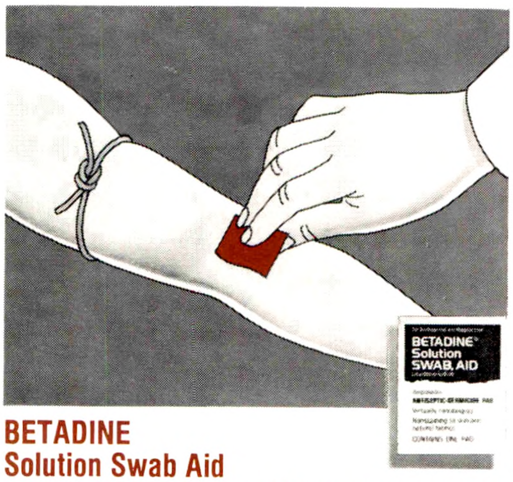

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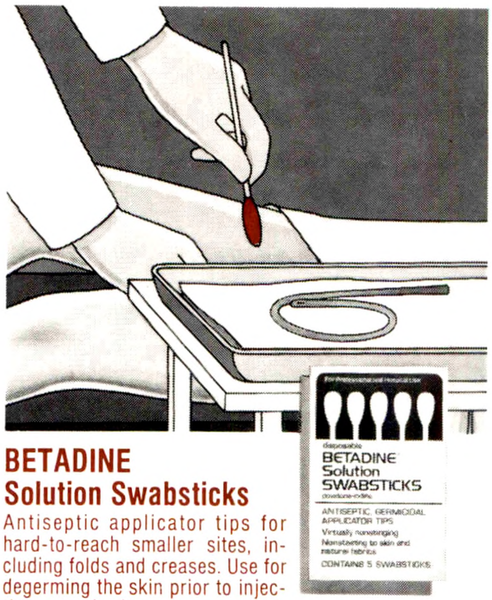

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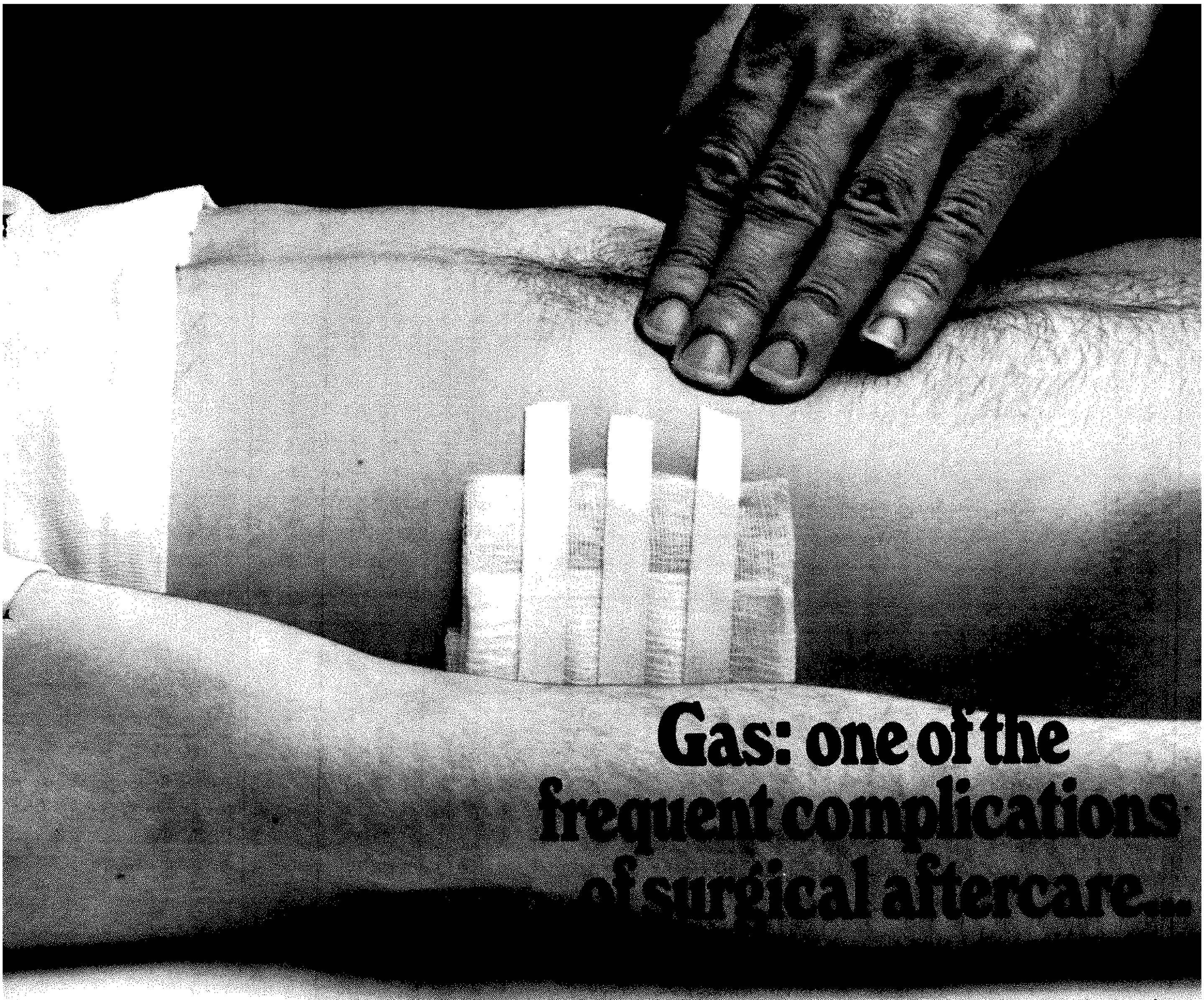

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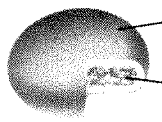

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol.* 38:386, Sept. 1971.
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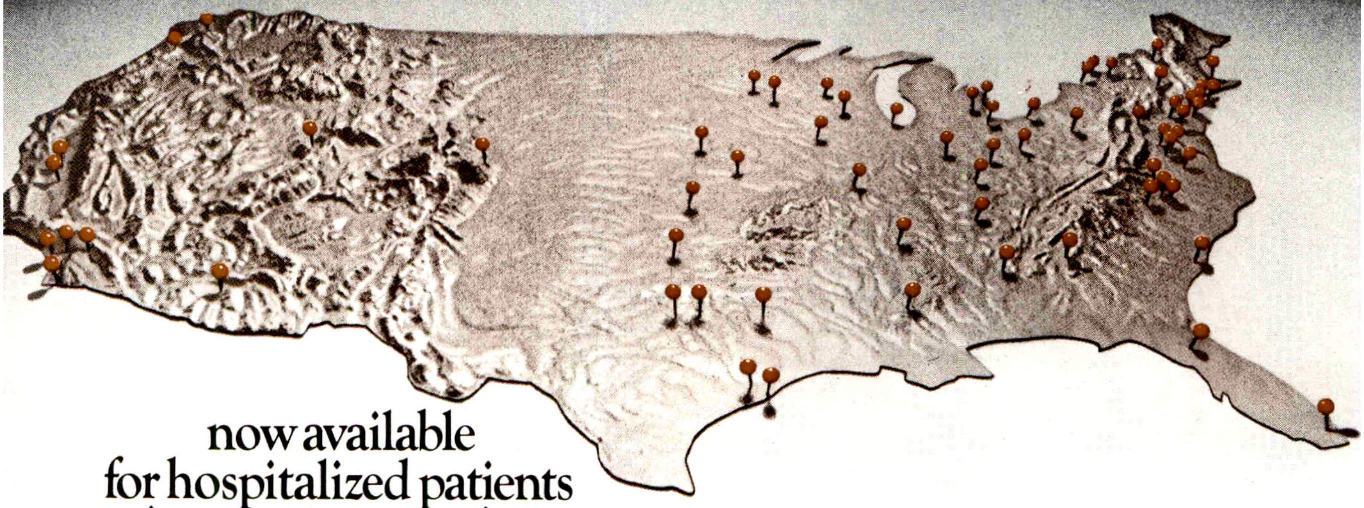

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urinary tract infections

Nebcin is indicated in the treatment of serious complicated and recurrent urinary tract infections. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

caused by susceptible strains of

Pseudomonas aeruginosa
Klebsiella-Enterobacter-Serratia group
Escherichia coli
Proteus sp. (indole-positive and indole-negative)
Providencia sp.
Citrobacter sp.
Group D streptococci
Staphylococci,* including *Staphylococcus aureus* (coagulase-positive and coagulase-negative)

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* Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Please see following page for summary of prescribing information.

Nebcin® ◆ I.M./I.V.
tobramycin sulfate

Prescribing Information

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, and colistin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., group D streptococci, and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: See WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg./Kg.). The possibility that these phenomena may occur in man should be considered if tobramycin is administered to patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg./Kg./day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg./Kg./day administered in three or four equal doses. This dosage should be reduced to 3 mg./Kg./day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg./Kg./day may be given in two equal doses every twelve hours. The usual duration of treatment is seven to ten days.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg./Kg., subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.[*] To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg./Kg. q. (6 × serum creatinine) h.

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of twenty to sixty minutes.

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[*] An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function (Dosage at Eight-Hour Intervals)

For Patient Weighing		Usual Dose for Serious Infections 1 mg./Kg. q. 8 h. (Total, 3 mg./Kg./day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg./Kg. q. 8 h. (Total, 5 mg./Kg./day)	
Kg.	Lb.	**mg./dose q. 8 h.**	**ml./dose[†]**	**mg./dose q. 8 h.**	**ml./dose[†]**
120	264	120 mg.	3 ml.	200 mg.	5 ml.
115	253	115 mg.	2.9 ml.	191 mg.	4.75 ml.
110	242	110 mg.	2.75 ml.	183 mg.	4.5 ml.
105	231	105 mg.	2.6 ml.	175 mg.	4.4 ml.
100	220	100 mg.	2.5 ml.	166 mg.	4.2 ml.
95	209	95 mg.	2.4 ml.	158 mg.	4 ml.
90	198	90 mg.	2.25 ml.	150 mg.	3.75 ml.
85	187	85 mg.	2.1 ml.	141 mg.	3.5 ml.
80	176	80 mg.	2 ml.	133 mg.	3.3 ml.
75	165	75 mg.	1.9 ml.	125 mg.	3.1 ml.
70	154	70 mg.	1.75 ml.	116 mg.	2.9 ml.
65	143	65 mg.	1.6 ml.	108 mg.	2.7 ml.
60	132	60 mg.	1.5 ml.	100 mg.	2.5 ml.
55	121	55 mg.	1.4 ml.	91 mg.	2.25 ml.
50	110	50 mg.	1.25 ml.	83 mg.	2.1 ml.
45	99	45 mg.	1.1 ml.	75 mg.	1.9 ml.
40	88	40 mg.	1 ml.	66 mg.	1.6 ml.

[†] Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules Nebcin® (tobramycin sulfate, Lilly) Injection, 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Ampoules Nebcin, Pediatric, Injection, 20 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Hyporets® (disposable syringes, Lilly) Nebcin Injection, 60 mg. (equivalent to tobramycin) per 1.5 ml., 1.5 ml., and 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., in packages of 24.

Each ml. also contains 5 mg. phenol as a preservative, 3.2 mg. sodium bisulfite, 0.1 mg. disodium edetate, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [063075]

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Clinical Echinococcosis

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In 221 patients (0.48% of hospital admissions) with hydatid disease (122 female and 99 male), 81% had single and 19% multiple organs involved. Lungs, liver and spleen as single sites of echinococcosis together represented 83.24% of cases and the liver alone represented 95.24% of instances with multiple organ involvement. One hundred seventy-nine single and 74 multiple cysts (ratio of 2.42/1) represented a total of 363 cysts (1.64 cysts/patient). The incidence of intact cysts was 51.52% and 48.48% had ruptured. Ruptures numbered highest in the lungs (73.44%) and greater in multiple (79.66%) than in single cysts (68.12%). In the liver, 27.14% of single and 54.55% of multiple cysts (40.44% of all liver cysts) had ruptured. Cysts varied in size from 0.8 to 35 cm diameter. Single cysts averaged significantly higher (14.16 cm) and multiple ones lower (5.71 cm) as did intact (6.75 cm) versus ruptured cysts (4.33 cm). Except for 10 silent and 15 symptomatic cysts treated medically, all the rest were treated surgically by removal of the endocyst or resection of both endo and exocysts including 205 first, 31 second and 5 third procedures (1.75% of all major operations). Complications occurred in 28.57%. Surgical mortality (3.57%) was markedly lower than with conservative treatment (60%) and significantly less than that of the whole group (14.48%).

HYDATID DISEASE is still a major health problem in infested areas of the world.[4,5,8,10,12] It can involve any organ and mimic almost any pathologic condition.[1] Its clinical manifestations concern practically all the medical and surgical specialists but namely the general surgeon because of the multiplicity and magnitude of the general surgical problems so often associated with human echinococcosis. Further studies are therefore needed to improve our understanding of the various clinical problems caused by this parasite in general, and more specifically, to reassess the surgical nature, complications and fatality of this disease in order to apply a more appropriate surgical treatment to clinical echinococcosis. In this investigation we have evaluated the clinical scope and surgical prevalence of hydatidosis in a retrospective study particularly covering organ distribution, multiplicity and pathology of this parasite.

Materials and Methods

This retrospective study covered a period of 7 years at the Saadi Hospital of Pahlavi University in Shiraz, Iran, from March 1964 to March 1971. We reviewed records of all patients admitted for more than 24 hours in the hospital. Special attention was paid to the surgical protocols but anesthesia tables, available x-rays and autopsy protocols were also studied separately from their respective files. Comparing informations obtained from various sources with those from the patients' records and final regrouping of these data prevented errors of omission or duplication.

Incidence

Hydatid disease involved various organs in 236 cases according to the hospital records but only in 221 patients was the diagnosis confirmed by either surgical exploration, post-mortem examination or both. During the study period, total hospital admissions numbered 46,449. Thus 221 or 0.48% of hospital admissions represented proved cases of hydatid disease.

Age and Sex

This series includes 122 female and 99 male patients with a mean age of 31.80 ± 11.72 years. Female patients were imperceptibly younger in the average (mean of

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TABLE 1. *Age Distribution*

Age per decade	Number of Patients Male	Female
1-10	0	0
11-20	14	28
21-30	28	34
31-40	40	38
41-50	15	9
51-60	1	7
61-70	1	6
Total	99	122

31.36 ± 13.32) than male patients (mean of 32.34 ± 9.41) but the difference had no statistical significance ($P > 0.05$). The fourth decade was the age of highest incidence in both male and female patients but the latters showed a comparative preponderance in the fifth, sixth and seventh decades (Table 1).

Diagnosis

As a high index of suspicion for echinococcosis is inherent to the medical practice in our area, a Casoni test, multiple x-ray examinations and organ scanning are considered practically in every patient suspected to be a possible host for hydatid cyst. In addition to this basic screening, angiography, tomography and bronchography have definitely helped to diagnose hepatic and pulmonary echinococcosis when plain x-rays have failed to demonstrate a characteristic pattern. Casoni skin test showed a positive yield from 62.5 to 100 per cent. These data are summarized in Table 2. Clinically, only hepatic echinococcosis showed a consistently recognizable pattern with abdominal mass and/or hepatomegaly, abdominal pain and sometimes jaundice. On the other hand, pulmonary hydatid cysts presented a diagnostic pattern in 91.49% of plain chest x-rays but greatly varying clinical manifestations. However, expectoration of hydatid fluid or cyst debris, or even bile rarely but firmly established the diagnosis of pulmonary echinococcal disease in cases of thoracobilia.[2] (Table 3) Diagnostic confirmation was finally reached by surgery in 189 patients, autopsy in 25 and both operation and post-mortem examination in 7 cases.

Organs Involved

Of 221 patients, 179 (81%) had single organ involvement and 42 (19%) showed multiple organs or sites involved by hydatid disease. Lungs, liver and spleen were the most common single sites of pathology having single or multiple cysts. In fact 149 patients (83.24%) harbored cysts of these three organs. Among multiple organs involved simultaneously, liver was outstanding and outnumbered all other organs or sites by containing single or multiple cysts in 40 of 42 patients (95.24%). Other organs and sites of single or multiple involvements are shown in Table 4 and 5.

TABLE 2. *Casoni Test in Hydatid Cysts*

Organs	Total Casoni tests	Casoni positive	%
Lungs	62	48	77.42
Liver	25	23	92.00
Liver and peritoneal cavity, sites unspecified	8	5	62.50
Spleen	5	5	100

TABLE 3. *Diagnosis of Echinococcosis*

Diagnostic means	Total	Number diagnostic	%
Casoni test, all organs	100	81	81.00
Plain chest x-ray	94	86	91.49
Plain abdominal x-ray	65	6	9.23
Thoracic tomogram	8	7	87.50
Expectoration of cyst fluid, debris or bile	5	5	100
Hepatic scan	4	3	75.00
Hepatic angiogram	2	2	100
Bronchogram	1	1	100

Single versus Multiple Cysts

We found 179 single (one cyst per organ) and 74 multiple cysts (more than one cyst in one organ). Thus single to multiple cysts presented a ratio of 2.42/1. In 6 patients multiple cysts were so numerous that an exact count could not be made by the surgeon. These cases were all abdominal and presumably included dozens of smaller cysts in the peritoneal cavity in addition to the known number involving other abdominal organs. Counting only the known numbers recorded by the operating surgeons, the 74 instances of multiple cysts per organ included a definite minimum of 184 individual cysts which together with 179 single cysts made up a total of 363 hydatid cysts in 221 patients (1.64 cysts per patient) (Table 6).

TABLE 4.

Single Organs Involved	Number of patients	%
Lungs	83	46.36
Liver	57	31.84
Spleen	9	5.02
Small bowel	7	3.90
Stomach	3	1.68
Pancreas	3	1.68
Kidney	3	1.68
Brain	3	1.68
Peritoneum	2	1.12
Prostate gland	2	1.12
Gall Bladder	1	0.56
Mesentery of Small Bowel	1	0.56
Omentum	1	0.56
Large Bowel	1	0.56
Heart	1	0.56
Femur	1	0.56
Urinary Bladder	1	0.56
Total	179	100

Intact and Ruptured Cysts

The total of 363 cysts included 187 (51.52%) intact and 176 (48.48%) ruptured ones. The greatest number of ruptured cysts were seen in pulmonary echinococcosis representing 94 of 128 cysts of lungs (73.44%). The proportion of ruptured single cysts was 47 of 69 (68.12%) and of multiple cysts 47 of 59 (79.66%). Liver cysts were less often ruptured. Of 136 liver cysts only 55 (40.44%) were recorded as ruptured. Ruptured single cysts were 19 out of 70 (27.14%) and multiple cysts 36 out of 66 (54.55%).

Size of Echinococcal Cysts

Descriptions giving dimensions of the cysts were only available in 110 single and 21 multiple hydatid cysts. The greatest size (35 cm diameter) and the smallest (0.8 cm diameter) were both observed in liver cysts. However, the smallest cyst with 0.8 cm diameter was only an autopsy finding and showed 1.2 cm difference from the smallest 2 cm size cyst observed clinically. Therefore this cyst is not included in the series for calculating the mean size of the clinically recorded diameters. The mean size (diameter) for single cysts was 14.16 ± 3.68 cm whereas it was 5.71 ± 3.21 cm for multiple cysts with a statistically significant difference ($P<0.05$). Single cysts with available information as to their size comprised 61 intact and 49 ruptured cysts and multiple ones included 12 intact and 9 ruptured hydatid cysts. The mean size of intact single cysts (15.02 ± 6.28 cm) compared to that of the ruptured ones (14.06 ± 4.73 cm) showed no statistically significant difference ($P>0.05$). However, in the multiple cysts, intact structures had a mean size of 6.75 ± 3.67 cm against that of 4.33 ± 1.87 cm for the ruptured cysts with a statistically significant difference ($P<0.05$).

Pathology

All patients except one had Echinococcus Granulosus. Although gross appearance of several multiple cysts simulated Echinococcus Multilocularis infestation, except in one instance no such diagnosis was made by the pathologist.

Grossly, infection accompanied all the ruptured cysts according to surgical protocols but valid bacteriologic proof was not established in any case because a primary culture was never obtained initially from the surgically sterile specimen. In fact bacteriologic reports either concerned cyst materials contaminated after surgery or discharges from surgically drained hydatid cysts or from surgical wounds. Thus surgeons' descriptions were to be relied upon as the only valid indication for the very early condition of the cyst being noted as infected or free from infection. Intact cysts were generally described as not being infected and only a few intact hepatic cysts were grossly suspected to have infection.

TABLE 5.

Multiple organs or sites involved	Number of patients	%
Liver and peritoneal cavity, sites unspecified	10	23.81
Liver and lungs	9	21.43
Liver and gastrohepatic omentum	6	14.29
Liver and spleen	3	7.14
Liver and porta hepatis	3	7.14
Liver and extrahepatic biliary ducts	2*	4.76
Liver, lung and peritoneum	1*	2.38
Liver, pancreas, spleen	1	2.38
Liver, omentum, pelvic peritoneum	1	2.38
Liver, diaphragm, mesentery of colon, peritoneum	1	2.38
Liver and stomach	1	2.38
Liver and diaphragm	1	2.38
Liver, Peritoneum, retroperitoneum, pelvic peritoneum	1	2.38
Lung, rib, vertebrae	1**	2.38
Pleura and rib	1**	2.38
Total	42	100

*One cyst per site or organ
**Involved by a single hydatid cyst

The exocyst, formed by the host organ, and the endocyst, proper to the parasite, presented two distinct structures in all patients. Even in ruptured and overtly infected hydatid cysts these two parts could be grossly distinguished. In only one pulmonary hydatid cyst no endocyst could be found at surgery. In this patient retrospective questioning revealed that the cyst should

TABLE 6.

Organs	Single hydatid cysts	Multiple hydatid cysts (2 to 9 cysts) per organ	Total number of cysts
Liver	70	66	136
Lungs	69*	59*	128
Spleen	7	12	19
Peritoneum and pelvic peritoneum	6	33	39
Small bowel	5	5	10
Stomach	3	2	5
Kidney	3	0	3
Brain	3	0	3
Pancreas	3	2	5
Prostate gland	2	0	2
Diaphragm	1	2	3
Mesentery of small bowel	1	1	0
Omentum	1	3	4
Large bowel	1	0	1
Gall bladder	1	0	1
Heart	1	0	1
Femur	1	0	1
Urinary bladder	1	0	1
Total	179	184	363

*Include two bilateral involvements

have been eliminated through expectoration prior to surgical exploration.

Complete or incomplete calcification of hydatid cysts was noted in 8 patients (3.62% of all patients). These cysts were all single and represented 2.20% of the total number of cysts. They involved the liver four times (4.12% of patients with liver cysts and 2.94% of liver cysts), the lungs twice (2.13% of patients with lung cysts and 1.55% of pulmonary cysts), once the spleen (7.69% of patients with cysts of the spleen and 5.26% of splenic cysts) and once the only cardiac cyst included in this series.

Silent Cysts

Clinically unsuspected and silent hydatid cysts, discovered at autopsy, were only found in patients suffering from other major pathology. In 10 such cases in this series, miliary tuberculosis had caused death in three, bronchopneumonia in another three, malignancy in two, postnecrotic cirrhosis in one and pulmonary embolism in the last patient. None of these patients had a pulmonary hydatid cyst and except two, one with retroperitoneal and another with splenic involvement, the remaining 8 patients had single or multiple hepatic echinococcosis, 4 of whom also showed splenic involvement.

Surgical Prevalence

During the 7 years of this study period 11, 712 major surgical operations were performed excluding procedures done under local anesthesia. This number included 205 primary procedures in 196 patients as the initial treatment and 36 reoperations (31 second and 5 third procedures) for complications of echinococcosis. Thus, the first surgical attempt to treat hydatid disease represented 1.75% of all major operations and surgery for completing the treatment or treating complications of echinoccosis accounted for 0.31% of the major procedures and 36 of 196 or 18.37% of surgically treated patients. Together the initial and the subsequent procedures counted 241 or 2.06% of all major operations. From another point of view, as only two patients in this study revealed to have abdominal hydatid cysts at exploratory laparotomy performed for recurrent abdominal pain and suspicion of neoplasm, echinococcosis justified surgery initially in 194 patients (98.98%) and ultimately in two (1.02%).

Surgical Treatment

A detailed account of the surgical treatment of our cases is beyond the scope of this paper but our review showed that the principle of surgical therapy, total excision of the cyst or cysts inasmuch as compatible with ease and safety, was adhered to by all 38 surgeons and senior residents who performed the operations. Furthermore, for rather simple cases of single small or average size cysts, results did not vary with technical preferences of the operating surgeons. Application of cryosurgical methods as already reported from this center[9] was very successful in small cysts. Plain surgical dissection and excision was also equally good in small and average cysts in general but less so in larger cysts as with cryosurgery. Concerning the two major organs, liver and lungs, resectability was nearly 100% for single cysts. However, for multiple liver cysts, resectability was only about 40% whereas it still approached 100% in the few multiple and bilateral lung cysts included in this series which were treated by single or staged operations. Resection of liver cysts resulted in a remaining cavity after removal of the endocyst which necessitated drainage for an average of 7 to 12 days postoperatively but usually much longer. Lung cysts however required the usual postoperative pleural drainage as for all thoracic operations. The cavity remaining in the lung parenchyma after excision of the cyst was generally closed by endoplication after suturing of individual bronchial openings. In a few instances the remaining cavity was left open and gradually became expanded and ultimately leveled with the rest of the normal lung as evidenced on postoperative x-rays. Only a few large cysts of more than 10 cm diameter left a persistent cavity behind several months after excision as seen on x-rays taken in the outpatient clinics.

Complications

Postoperative complications ranged from simple superficial wound infection to hemorrhage, anaphylactic shock, peritonitis, subphrenic abscesses, draining sinuses after resection and drainage of hepatic hydatid cysts and wound dehiscence in abdominal echinococcosis. In thoracic cases, persistent pneumothoraces, empyemas and bronchopleural fistulas, thoracobilia, wound infections and persistent partial atelectasis constituted the postoperative complications. Grossly 56 patients (28.57%) showed one or more postoperative complications, 36 of whom required reoperation and seven died.

Of the 25 non-surgical patients, 10 were clinically silent but 9 of the 15 symptomatic patients had fatal complications. These complications consisted of spontaneous or traumatic rupture of abdominal hydatid cysts with generalized peritonitis in three and subphrenic abscesses in two. The other four patients had pylephlebitis, portal hypertension caused by liver echinococcosis with esophageal variceal bleeding, ruptured liver hydatid cyst with choledochal obstruction and ruptured cardiac hydatid cyst with cardiac tamponade.

Morbidity and Mortality

The hospital stay of our patients ranged from 8 to 110 days with a mean of 18.71 ± 14.92. For the 196 surgical patients the mean hospital stay was 17.98 ± 15.36 which was not statistically different from that of the whole group ($P>0.05$) but was significantly shorter than the calculated means of 24.48 ± 9.28 days for the 25 non-surgical patients and of 29.40 ± 12.17 days calculated separately for the 10 patients with silent echinococcoses ($P<0.05$). On the other hand 156 surgical patients who had only one operation showed a mean hospital stay of 13.19 ± 3.26 days which was much shorter ($P< 0.05$) than those of 35 patients with 2 operations (30.17 ± 21.50 days) and another 5 with 3 operations (78.80 ± 20.39 days). When means for postoperative periods were calculated it was shown that the 205 primary procedures were associated with a mean of 10.78 ± 5.08 postoperative days but the 36 reoperations presented a mean of 17.11 ± 15.58 days and the difference was significant ($P<0.05$). Also, considering patients who had one operation and those who had two and three procedures (nine with primary two procedures and 31 with secondary operations), the postoperative means were significantly shorter for the first group compared with the second and the second group compared with the third (Table 7). Thus, the length of hospital stay was directly proportional to the complexity of cases implying longer preoperative work-up and more significant complications and to the number of operations.

The mortality in this series was represented by 32 deaths in 221 patients (14.48%). However, only 7 deaths occurred in the 196 surgical patients postoperatively which indicates a total surgical mortality of 3.57%. Causes of deaths were operative and postoperative uncontrollable bleeding in two patients with massive liver resection, thoracobilia with aspiration of bile in another two, postcraniotomy cerebral edema, dehiscence of bronchial suture with bronchopleural fistula and anaphylactic shock after operative rupture of an abdominal cyst in the remaining three patients.

Deaths in patients with one, two and three operations respectively numbered four, two and one, representing a mortality of 2.56%, 5.71% and 20%. On the other hand, non-surgical patients included 10 cases of silent hydatid disease only discovered at autopsy and 15 others with clinical manifestion but also proved by autopsy. This identifies 25 non-surgical patients with an apparent mortality of 100%. However, as initially 236 patients justified the clinical diagnosis of hydatid disease, in addition to 221 patients who had a confirmed diagnosis, 15 others could have harbored the disease with diagnostic confirmation. Therefore a minimum of 40 patients (25 autopsy proved and 15 unconfirmed) may be considered to represent total non-surgical cases with a mortality of 25/40 or 62.5%. On the other hand, considering that fatal complications caused by or directly related to echinococcosis occurred in 9 of the 15 symptomatic patients a more realistic non-surgical mortality would be 9/15 or 60%.

Discussion

This study confirms that echinococcosis is still a major clinical problem and in spite of recent advances in diagnostic and therapeutic means, hydatid cysts may still present a considerable morbidity and a significant mortality. That hydatidosis is primarily a surgical disease, is shown in our study beyond any doubt. In fact if treated surgically both morbidity and mortality should considerably drop as seen by comparing surgical and non-surgical results in this series. The most interesting difference is between the non-surgical mortality of about 60% and less than 4% for our surgical cases and for a closely similar figure reported by others.[8] A definite point of emphasis revealed by this study is the highly fatal evolution among hospital patients with symptomatic hydatidosis treated non-operatively.

There is a period of silent growth in the natural history of this parasite when no clinical manifestation should occur e.g. in the 10 silent cases in this study and as reported in another recent study.[5] These instances would not have been discovered were it not for another major disease invariably present and causing death in all our silent cases. This may implicate an increased susceptibility to hydatid infestation caused by a major debilitating disease. Nevertheless, and irrespective of the factors involved, after the silent period is over, beginning of clinical manifestations forms a decisive turning point with a changing prognostic significance that if not treated

TABLE 7.

	Surgical patients			
Hospitalization Time and Mortality	196 patients	156 with 1 operation	35 with 2 operations	5 with 3 operations
Preop stay (days)	3.65 ± 2.93	3.30 ± 2.56	4.34 ± 2.89	9.6 ± 6.39
Postop stay (days)	11.76 ± 7.89*	9.97 ± 2.37	13.19 ± 11.39**	23.73 ± 12.83†
Total hospital stay (days)	17.98 ± 15.36	13.19 ± 3.26	30.17 ± 21.50	78.80 ± 20.39
Mortality	7 (3.57%)	4 (2.56%)	2 (5.71%)	1 (20%)

* in 241 operations
** in 70 operations
† in 15 operations

by surgical extirpation the disease is no longer a harmless condition and may carry a forbiddingly high rate of fatal complications.

Predominance of single pulmonary involvement over single liver hydatidosis in this series matches similar findings by others reporting on echinococcosis in Iran[7] and makes one consider that the lungs could act as a primary filter if some special conditions prevail. Such environmental factors as scarcity of rainfalls and dusty atmosphere in the south could make an air-born respiratory infestation possible which would explain the southern preponderance of pulmonary hydatid cysts as opposed to the northern majority of hepatic echinococcosis in Iran. Reports from mediterranean countries and other regions of geographic environment similar to northern Iran also indicate a uniformally greater hepatic infestations.[8,10,11]

Complexity and variability of clinical echinococcosis are characteristic features of this disease. Except in pulmonary and hepatic echinococcosis, finding a definite pattern is impossible and often diagnosis is only established by surgical exploration or post-mortem examination. Occasionally the parasite changes the physiologic function of the involved organ significantly and further obscures the diagnosis so that even pulmonary or hepatic diseases, of otherwise typical form, became unrecognizable. Thoracobilia,[2] pulmonary embolism, cavitary lung lesions with hemoptysis and obstructive jaundice and portal hypertension with bleeding esophageal varices are some examples of such complex clinical pictures observed in our study. However, most of the lung and liver hydatids present recognizable features as evidenced in this study (Table 3) and in fact none of the silent cases included a lung cyst and those with liver involvement harbored liver cysts far below the average size. Thus in the silent cases the sine qua non of diagnosis, radiologically visible and clinically palpable cysts of the pulmonary and hepatic locations were absent.

Diagnostic value of the Casoni skin test has been considered as firmly established with an accuracy of about 90%.[6,12] False negatives in our series varied from zero in splenic cysts to 37.5% in cysts of the abdominal cavity involving liver and peritoneum of unspecified sites. False positive Casoni tests could not be ascertained in our study but an approximate figure may be obtained by considering 6 positive intradermal reactions in 7 unconfirmed cases tested, i.e., 6 false positive in a total of 107 patients tested or 5.61%. This is markedly less than a 10-15 per cent false positive tests reported in other studies.[3,6]

Regarding the three major sites, liver, lungs and spleen, the yield of positive Casoni was lowest with pulmonary, higher with liver and highest with splenic echinococcosis. Neither the predominance of multiple over single, nor that of ruptured over intact cysts explained this difference for which the greater immunoactivity of the liver and spleen may be responsible. Other tests such as complement fixation, latex agglutination, passive hemagglutination and indirect fluorescent-antibody[6] were not used in this series.

Cyst size and its correlation with intact versus ruptured status and single versus multiple structures in this series revealed that factors contributing to rupture may include a greater diameter of the cyst but are definitely related to multiplicity of the cysts and pliability or elasticity of their host organ. Thus multiple lung cysts included the largest and single liver cysts the smallest number of ruptures.

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Total Esophageal Reconstruction After Extraction of the Esophagus

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During the period between 1971 and 1974, 25 cases of carcinoma of the hypopharynx and cervical esophagus underwent esophageal extraction and total esophageal reconstruction without operative mortality. The operative methods used for this series were blunt dissection, or everting stripping of the thoracic esophagus without thoracotomy followed by pharyngogastro or -colostomy as a one stage procedure via a posterior mediastinal route created by esophageal extraction. The operative technique of esophageal extraction without thoracotomy is described. It is obvious that mediastinal tunnel is the shortest route through which to put the chosen organ for esophageal substitution. This operation is to be recommended for lesion of the hypopharynx and cervical esophagus as well as some esophageal stricture because of its operative simplicity, ease, safety and rare postoperative complications.

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THE HISTORY of total esophageal reconstruction after resection of the hypopharynx or cervical esophagus originated with skin grafts or skin tube implantation as practiced in the field of plastic surgery. This has been followed by surgical attempts using a colonic segment or the stomach with considerable difficulty.

This is a report of a series of patients with carcinoma of the hypopharynx and cervical esophagus which underwent esophageal reconstruction after extraction of the thoracic esophagus. Some technical points are discussed, i.e., blunt dissection or stripping of the thoracic esophagus without thoracotomy, and the technique of preserving the larynx in carcinoma of the cervical esophagus. The operative results are reported.

Materials

Twenty seven cases of carcinoma of the hypopharynx and cervical esophagus were admitted to the Toranomon Hospital during the period 1971 to 1974. Of the 27 cases, resection of the tumor and total reconstruction of the esophagus with immediate pharyngogastrostomy or pharyngocolostomy after extraction of the esophagus was carried out on 25 cases. Resectability was 92.6% which was fairly high since this operative approach is also applicable for rather advanced cases (Table 1). Most cases were preceded by preoperative irradiation in dosages of approximately 3000-4000 rads.

Method

The completed forms of the procedure are shown schematically in Fig. 1. The skin incisions are made only in the neck and upper abdomen. Thoracotomy is not necessary. The thoracic esophagus is extracted upwards or downwards by blunt dissection, or by everting stripping. The mobilized stomach or colon is brought through this newly created posterior mediastinal tunnel, up to the chin and anastomosed to the hypopharynx. This total esophageal reconstruction consists only of pharyngogastrostomy and pyloroplasty and is very simple in form when the stomach is used.

Procedures in the Neck

With Combined Resection of the Larynx. The operation is started from the neck. A U-shaped skin incision is preferred because of wide exposure and postoperative cosmetic advantage. Complete lymph node dissection in the neck is performed. The trachea is transected at the normal portion, the distal end is sutured to the skin and another sterilized endotracheal tube is inserted into the tracheostomy. This is then handed over to the anesthetist. The hypopharynx is opened above or below the hyoid bone. After opening the pharynx, lavage of the lumen is done to prevent contamination of the surgical

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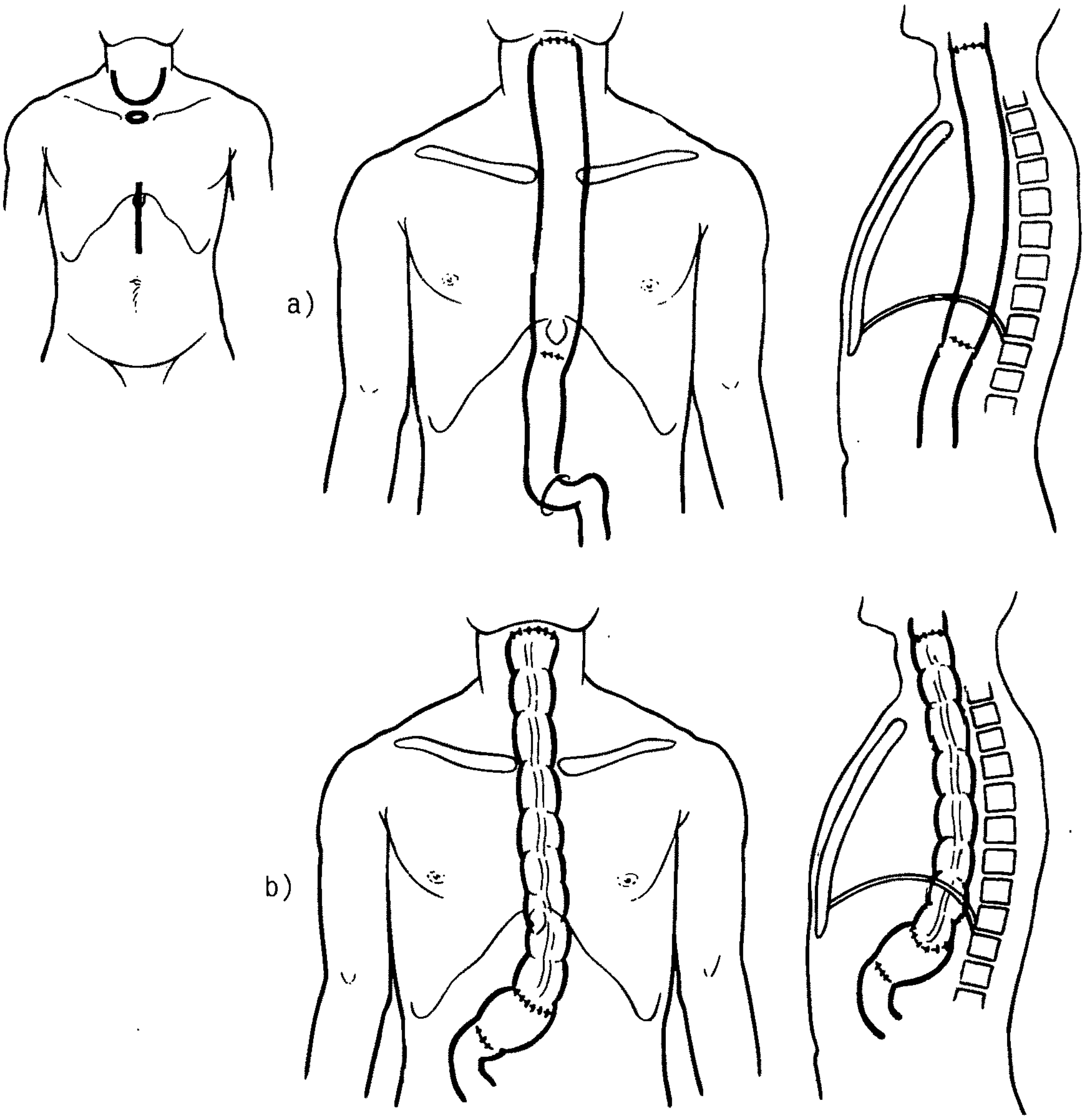


FIGS. 1a and b. Total esophageal reconstruction after extraction of the thoracic esophagus. (1a) Pharyngogastrostomy, (1b) pharyngocolostomy.

field and tumor safe surgical margin is ascertained. Then, the mass containing the pharyngeal tumor and the larynx is separated from the oral pharynx en bloc and wrapped in a towel.

With the Larynx Preserved. Special attention should always be paid as to whether the larynx can be preserved or not. When one attempts to preserve the larynx for carcinoma of the cervical esophagus, one should be very careful not to traumatize the bilateral recurrent laryngeal nerves. With traction on a tape put around the cervical esophagus, dissection between the trachea and esophagus is continued up to the level of cricoid cartilage, taking care not to traumatize the cricoid muscles (Fig. 2). One may feel a tumor and some normal part of the esophagus between the proximal border of the tumor and the larynx, but this is gross limits at best. After exposing the whole esophagus by blunt dissection as described later, esophagotomy[4] must be placed to ensure safe surgical margin even after considering suturing width (Fig. 3). Biopsy of the resected margin is naturally added if deemed necessary. Then the esophagus is transected just below the larynx for anastomosis.

Blunt Dissection of the Thoracic Esophagus

The esophagus can be extracted by the following three methods.

1. Blunt Finger Dissection: Blunt finger dissection along the esophageal adventitia is carried out from both the mediastinal superior aperture and the esophageal hiatus. Bilateral main esophageal branches of the vagus nerve are severed after hooking them with index finger. The entire thoracic esophagus may be extracted upwards (Fig. 4a).

A part of blunt dissection can be carried out with the aid of ring dissector. The ring is put around the esophagus and pushed distally by an attached bar using counter traction of the esophagus. After this auxiliary procedure, the entire esophagus may be extracted either upwards or downwards (Figs. 4b and 5).

2. Eversion Stripping: Another easy way to dissect the

TABLE 1. *Cases of Carcinoma of the Hypopharynx and Cervical Esophagus.*

		Carcinoma of the Hypopharynx	Carcinoma of the Cervical Esophagus	Total
No. of Cases		24	3	27
No. of Resection and Reconstruction		22	3	25
Gastrostomy only		2	0	2
Combined Resection of the Larynx	Resected	22	0	22
	Preserved	0	3	3
Organs used for Esophageal Substitution	Stomach	21	3	24
	Colon	1	0	1
Operative Mortality		0	0	0

esophagus using a vein stripper is shown in Fig. 4c. A vein stripper is inserted into the lumen of the thoracic esophagus through the small hole made on the abdominal esophagus. This is pushed up until it is felt from the neck. The tip of the stripper is allowed to perforate the esophagus and the cap is put on its end. The esophagus is firmly tethered with a heavy tie to the stripper at the level just below the perforation (Fig. 6). The esophagus is then transjected above the cap. Then, the stripper is pulled downwards. The entire thoracic esophagus can be removed with the mucosal surface everted (Fig. 7) One must not forget to place a tape through the posterior mediastinum prior to removal of the esophagus for the purpose of bringing the stomach or colon up to the neck.

Abdominal Procedure

A proximal median incision is made in the abdomen. The entire greater curvature of the stomach is dissected free. The right gastric and gastroepiploic arteries and veins are preserved. Then the left gastric artery and vein are cut at their roots to preserve the anastomosis between the right and left gastric artery for cardiac blood supply from the right gastric artery. Dissection is continued towards the esophageal hiatus and the abdominal esophagus is exposed. Pyloroplasty is always added. Then the abdominal esophagus is divided. The cut end of the gastric cardia is closed in two layers.

When the stomach cannot be used, the colon is mobilized for esophageal substitution preferably in isoperistaltic fashion.

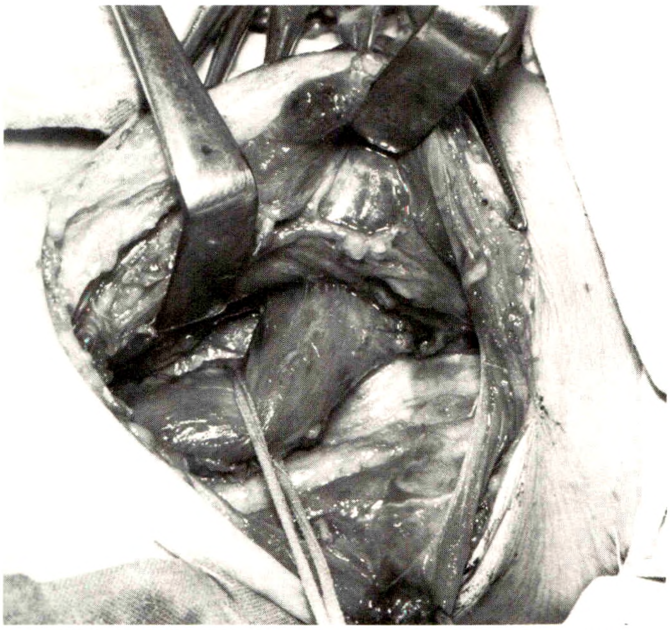


FIG. 2. The tissue between the trachea and esophagus is dissected up to the level of the cricoid cartilage when the larynx can be preserved.

Elevation of the Stomach or Colon for Esophageal Substitution and Anastomosis

The stomach or colon is then pulled up to the pharynx through the posterior mediastinal tunnel (previous esophageal bed) by pulling the tape anchored to the stomach or colon. The next step is the anastomosis between the oral pharynx and the stomach or colon. Two layer anastomosis[3] is performed: mucosa to mucosa and

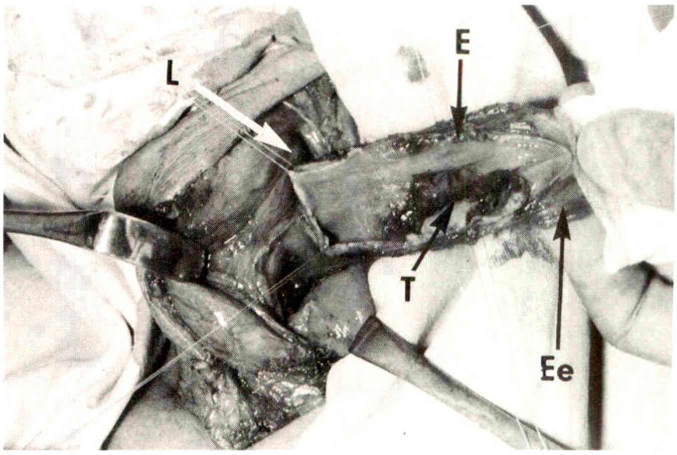


FIG. 3. A safe surgical margin is ensured, at least, by direct vision through esophagotomy (the larynx being preserved). L: larynx; E: esophagotomy; T: tumor; Ee: extracted esophagus.

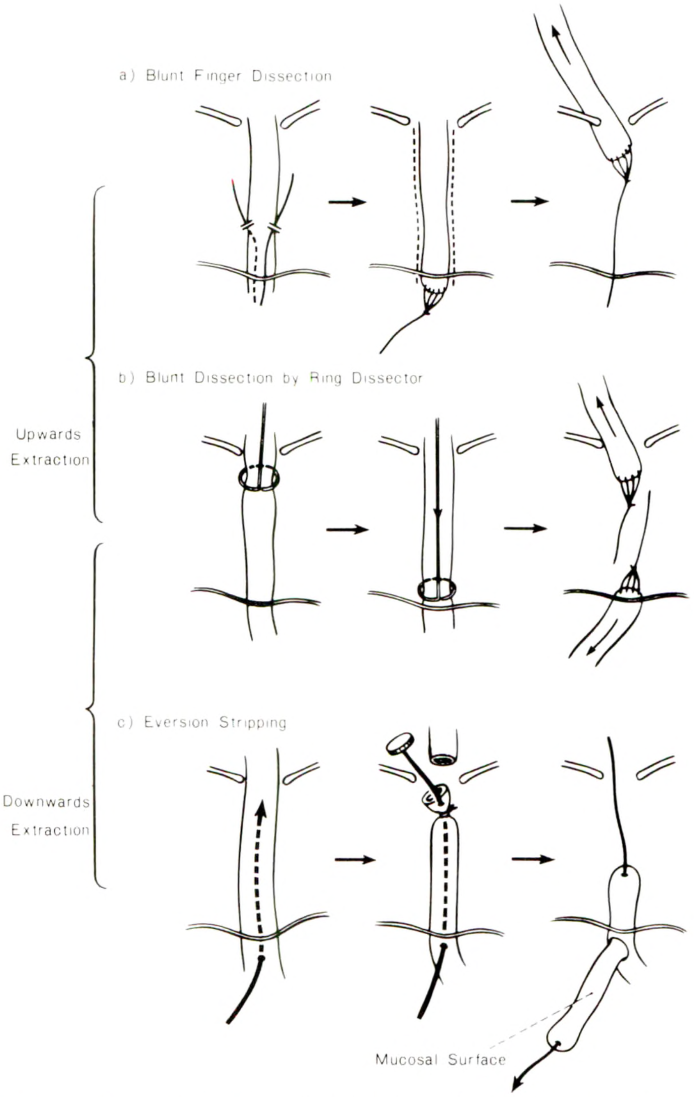


FIG. 4. Methods of dissecting the thoracic esophagus without thoracotomy.

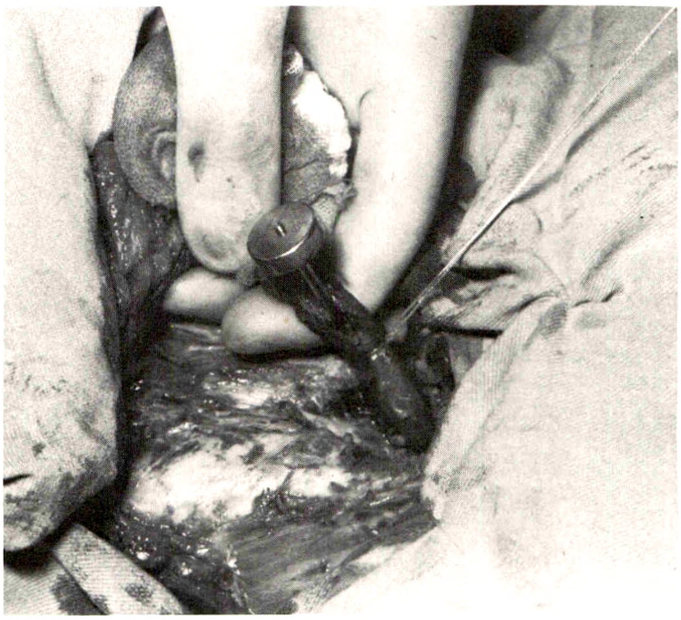


FIG. 6. For eversion stripping of the esophagus, a vein stripper has been installed in the esophagus (neck).

seromuscular to pharyngeal muscular layers. Fig. 8 shows completion of pharyngogastrostomy.

Results

During the period from 1971 to 1974, 25 cases of this kind of operation were performed without a single operative death. Of 25 cases, a postoperative salival fistula developed in only one patient who had an unusually small stomach. This healed spontaneously and the patient is now doing well. Usually, oral ingestion is started on the 9th postoperative day and all patients tolerated a regular diet. The most common postoperative problem was occasional regurgitation of ingested food (the phenomenon of "overflow"). But it usually disappears in a couple of

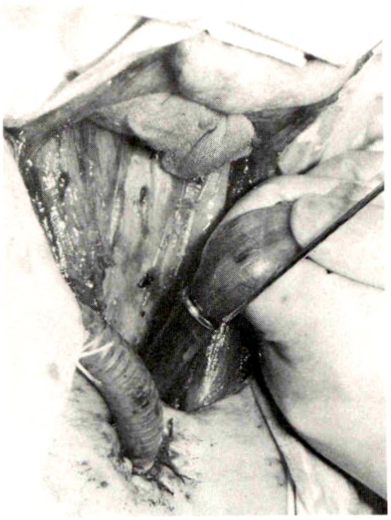


FIG. 5. Ring dissector is placed around the esophagus in the neck.

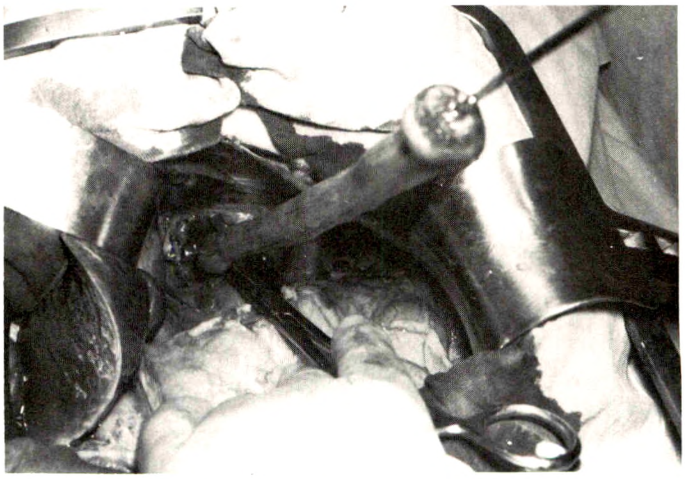


FIG. 7. The entire thoracic esophagus is easily extracted with the mucosal surface everted by pulling down the vein stripper (abdomen).

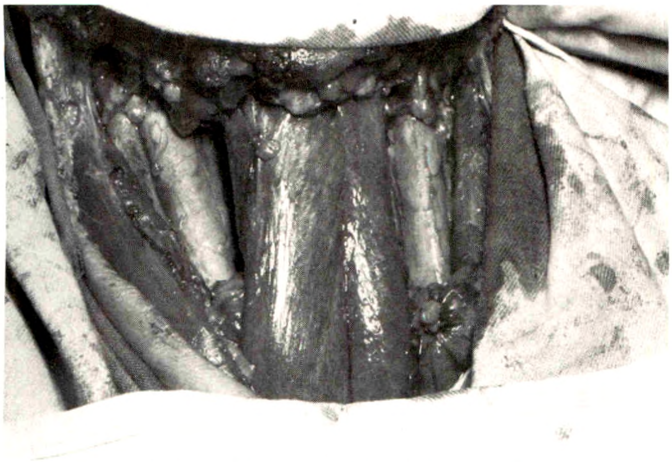


FIG. 8 Completion of pharyngogastrostomy.

months. The longest survival is a patient who is well at 3 years and 7 months after surgery, and the shortest 3 months. Satisfactory long term results may not be obtained because this procedure has been often used only for palliative purposes.

Figs. 9a and b are the postoperative x-rays of pharyngogastrostomy and Fig. 10 shows the stomach placed in the posterior mediastinum. The stomach is always the first choice as an organ for esophageal substitution, but in one case the isoperistaltic colon was used because of a large ulceration of the stomach which was also resected (Fig. 11).

Discussion

Great efforts have been made in reconstructive surgery of this region.[1,5-10,12,13] Except for a small defect, the technique of skin grafting is usually multistaged, postoperative fistulae formation are not rare and early oral ingestion of food tends to be unpredictable.

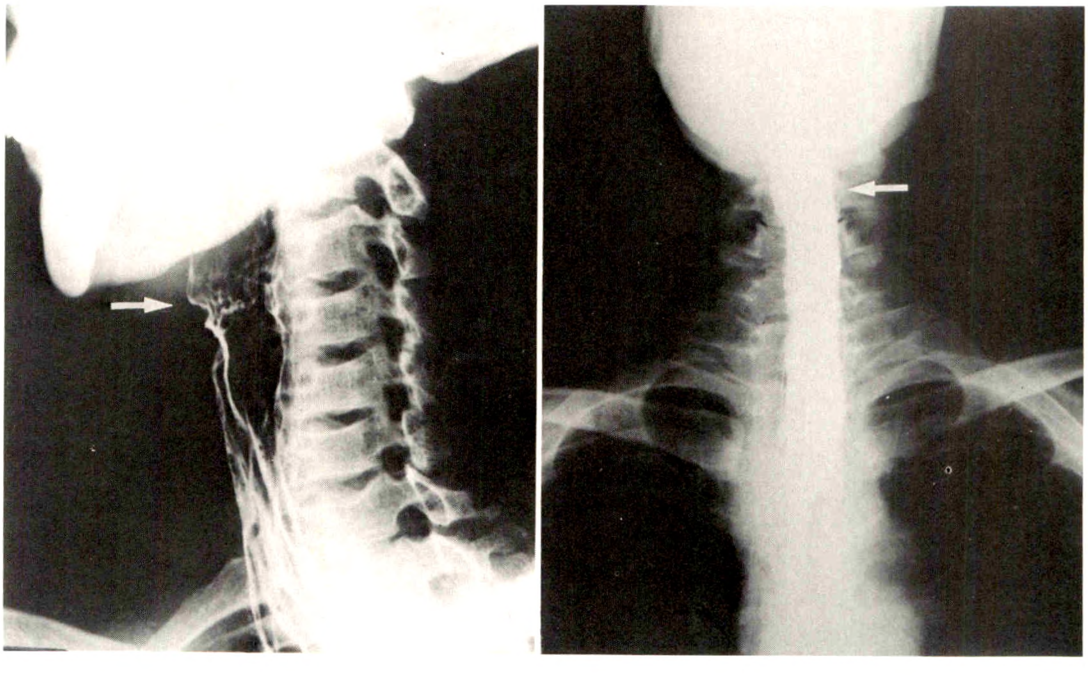
Free transplantation of a segment of small intestine or colon with vascular anastomosis[8,10] has been proposed but at present, this remains rather unpractical and is not to be recommended as an established procedure for the majority of surgeons.

Direct anastomosis between the pharynx and the distal end of the resected esophagus was done by Wooler[13] and Jack.[6] Later, this was not recommended because of poor circulation at the cut margin of the esophagus and severity of the operation.

Total esophageal substitution with colon[5] has been rather common way of reconstruction, but it contains at least 3 anastomoses and there is a greater chance of contaminating the surgical field. The stomach is considered to be the organ of choice for esophageal substitution. It is not necessary to redesign the stomach but the whole natural stomach is best used as the total esophageal substitution.

Blunt esophageal dissection without thoracotomy was reported by Turner[11] in 1936 for carcinoma of the thoracic esophagus, but it is not recommended for malignancies of the thoracic esophagus because of potential hemorrhage and the impossibility of mediastinal lymphnodes dissection. Later, this procedure has been applied successfully by several authors for carcinoma of the hypopharynx.[1,7,9]

In this paper, several operative procedures and techniques are reported. Particular attention is paid to the techniques of blunt dissection of the esophagus with fingers or ring and everting or turn over stripping of the esophagus using vein stripper. Some technical points in



FIGS. 9a and b. Postoperative barium swallow. Arrows show pharyngogastrostomy. (a) Double contrast picture, (b) barium-filled picture.

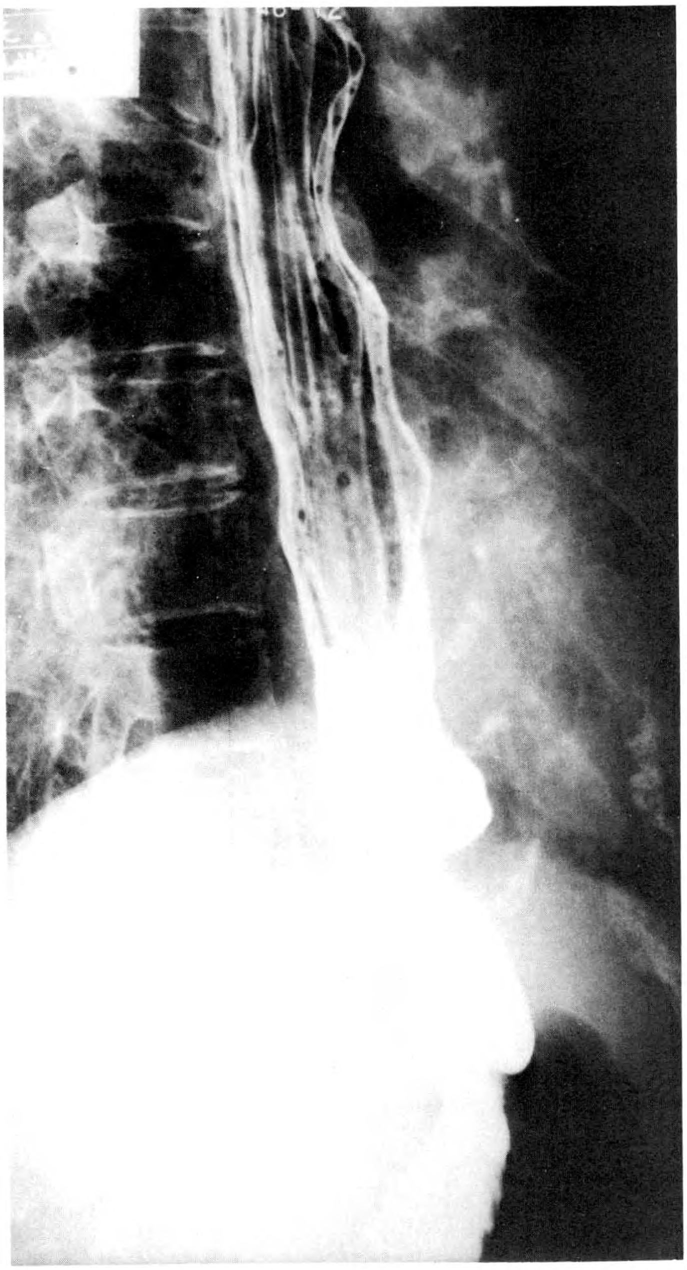


FIG. 10. Postoperative barium swallow. The entire stomach in the posterior mediastinum is demonstrated.

preservation of the larynx for carcinoma of the cervical esophagus are described. The esophagus can be extracted either upwards or downwards. Blunt finger dissection is an upwards extraction, and everting stripping is a downwards extraction and the level of esophageal transection before extraction must not contain a tumor itself or its intramural invasion. The operator should choose the means of esophageal extraction according to the location and extent of esophageal lesions. No hemorrhage or pleural tearing has occurred in this series. Pharyngo-gastrostomy is relatively simple. In some occasions, pharyngo-colostomy by the same route should be applied when the stomach cannot be used (i.e.; postgastrectomy or with a gastric lesion such as ulceration). The stomach should always be the first choice as esophageal substitution for its great size, ample vascularity and operative simplicity. This procedure is rather simple and can even be applied for palliative reasons to relieve dysphagia or dyspnea secondary to a malignancy. Consequently, satisfactory survival rate after this procedure cannot be expected, but still remains useful for the lesion and sometimes for carcinoma of the gastric cardia or a benign stricture of the esophagus.[2]

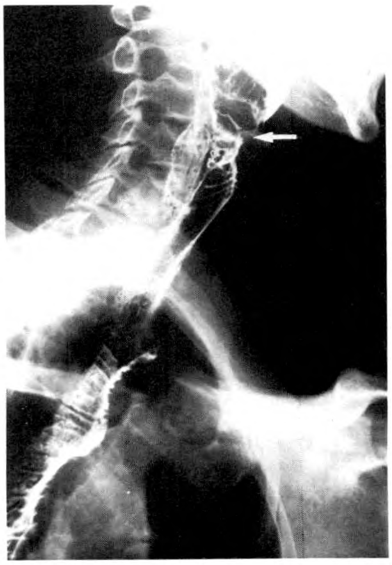


FIG. 11. Postoperative barium swallow. The arrow shows pharyngocolostomy.

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Peripheral Intravenous Infiltration Necrosis

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Peripheral extravasation of intravenous solutions containing calcium salts and/or 10% dextrose has caused significant local tissue necrosis in 8 patients, including 6 infants. These incidents prolonged hospitalization and in 5 cases caused severe disfigurement or imperiled limb function. Treatment followed established principles of debridement, early skin grafting and secondary reconstruction as needed. While intravenous alimentation or the administration of calcium salts is often indicated by the clinical situation, the physician administering these drugs must realize that extravasation may cause serious sequelae.

PERIPHERAL INTRAVENOUS INFUSIONS are an essential and seemingly innocuous adjunct in the management of ill patients. The common local complications of peripheral infusions, phlebitis and superficial thrombosis, seem trivial and easy to manage when compared with the hazards of central venous catheterization for hyperalimentation. However, many physicians are not aware that peripheral extravasation of calcium salts and 10% dextrose solutions can cause extensive local tissue necrosis resulting in major and prolonged morbidity.

The Plastic Surgery Service at Walter Reed Army Medical Center has treated eight patients, including 6 infants, in whom such extravasation led to significant tissue necrosis and the threat of functional and cosmetic impairment. These cases are described and discussed in order to increase physician awareness of the pathogenesis, management, and prevention of this iatrogenic injury.

Case Reports

Case 1. A 5-month-old severely malnourished Korean American infant received a solution containing amino acids, calcium gluceptate and 10% dextrose through a vein on the dorsum of the left hand. An infusion pump was used to regulate the rate of fluid administration, and the hand was splinted and covered with a dressing. The solution infiltrated and within a few hours the swollen hand had a pale necrotic area involving most of the dorsum (Fig. 1). The hand was treated by surgical excision of the eschar and chemical debridement with TRAVASE ointment.* (Fig. 2) On the 19th day after injury a full thickness skin graft from the abdomen provided good cover and extensor function in the hand was preserved (Fig. 3).

Case 2. A 2.5 kg male infant had closure of a tracheoesophageal fistula and a gastrostomy during the first 5 days of life. Postoperative infiltration of a 10% dextrose in water intravenous solution regulated by an infusion pump caused necrosis of skin and subcutaneous tissue on the dorsum of the left hand (Fig. 4). Mafenide acetate cream was applied topically while awaiting demarcation. Necrotic tissue was debrided surgically and with TRAVASE ointment. A split thickness skin graft was applied to the wound 22 days following injury. Satisfactory healing ensued and normal hand function was obtained.

Case 3. A 2.1 kg infant girl underwent surgical closure of a tracheoesophageal fistula and a gastrostomy. During the postoperative period a solution containing 10% glucose, electrolytes, and calcium gluceptate infiltrated and caused skin slough over the dorsum of the foot and ankle. This was treated with TRAVASE ointment and sharply debrided. The area was covered with a split thickness skin graft 3 weeks after injury with only a 60% take of the graft. Five days later the open area was covered with banked autograft and satisfactory healing occurred.

Case 4. A full term male infant had several seizures 18 hours after birth that were attributed to hypocalcemia. He was treated with calcium chloride given in 10% glucose in water via scalp veins. Infiltration resulted in bilateral frontotemporal scalp necrosis. Soon after transfer to Walter Reed Army Medical Center the necrotic tissue was debrided, including the outer table of the skull (Fig. 5). Following two weeks of local wound care, the scalp defects were covered with split thickness skin grafts. The resulting defects were reconstructed later in two stages using scalp rotation flaps.

Case 5. A premature newborn male infant of a diabetic mother was acutely ill from birth. He required vigorous treatment for respiratory distress, hypoglycemia, and hyperbilirubinemia. On the second day of

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*Bacillus Subtilis protease, Flint Laboratories.

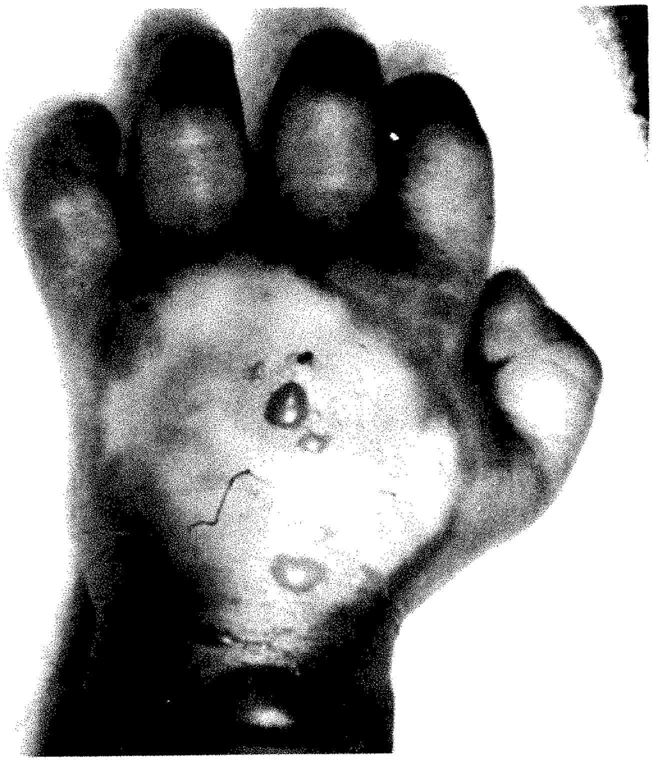

FIG. 1. Photograph shortly after discovery of infiltration of a 10% dextrose, calcium gluceptate and amino acid intravenous solution.

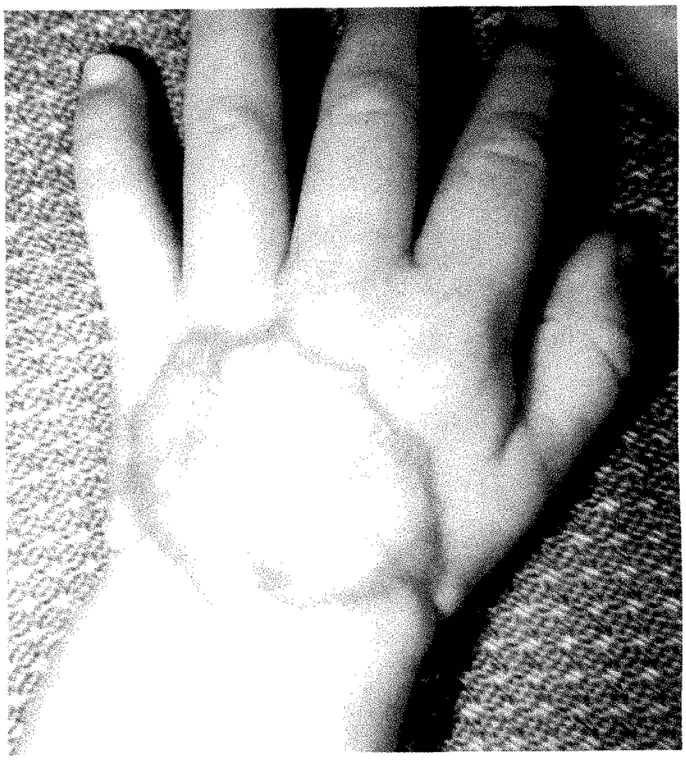

FIG. 3. Six weeks after grafting. Patient has full extensor function in fingers.

life, the patient was hypocalcemic and was given 2 mg of undiluted calcium gluceptate through a scalp vein. Infiltration caused a 10 x 12 mm area of necrosis (Fig. 6a). This was treated with dressing changes and sharp debridement, and healing occurred spontaneously (Fig. 6b).

Case 6. A 2 kg premature male had episodes of apnea and extremely poor gag and swallowing reflexes during the first week of life. Fluids were given by scalp vein infusion, regulated by a pump. Infiltration of 10% dextrose in water in the right temporal scalp led to necrosis of an area 10 x 13 mm. This healed spontaneously after surgical debridement.

Case 7. Soon after open heart surgery, a 42-year-old woman received an intravenous solution containing calcium chloride through a right frontal scalp vein. Some of the solution estravasated causing a 4 x 6 cm slough of forehead skin and scalp. The necrotic area was kept clean, debrided and gradually healed by ingrowth of scar epithelium.

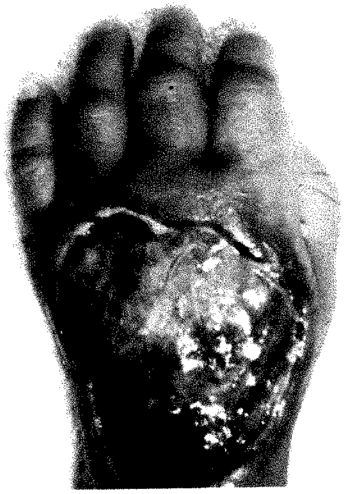

FIG. 2. Appearance of wound just prior to grafting.

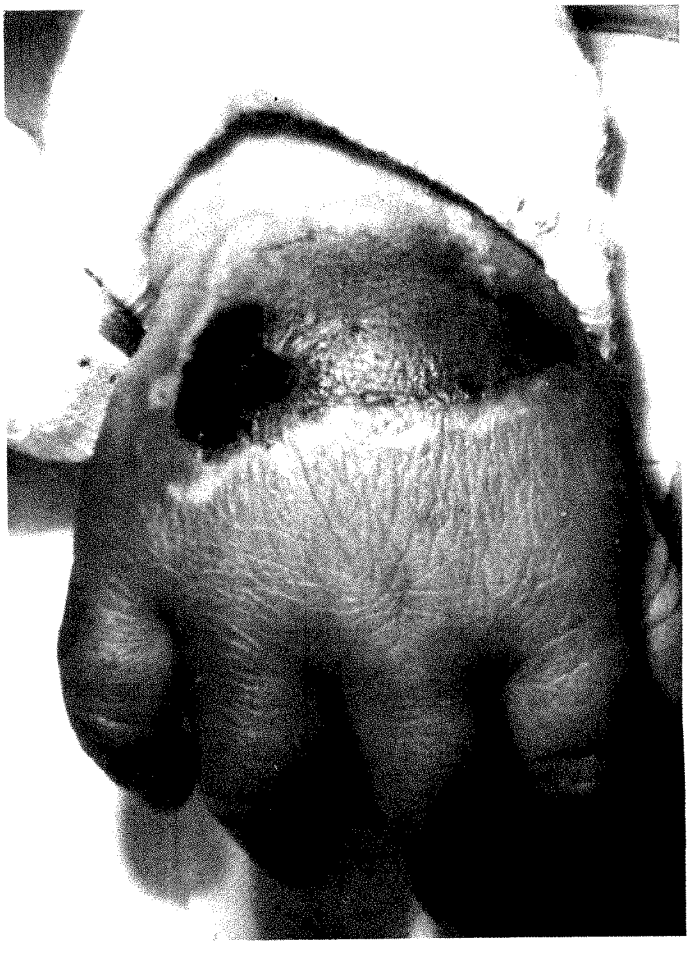

FIG. 4. Skin and subcutaneous tissue necrosis following infiltration of a 10% glucose solution.

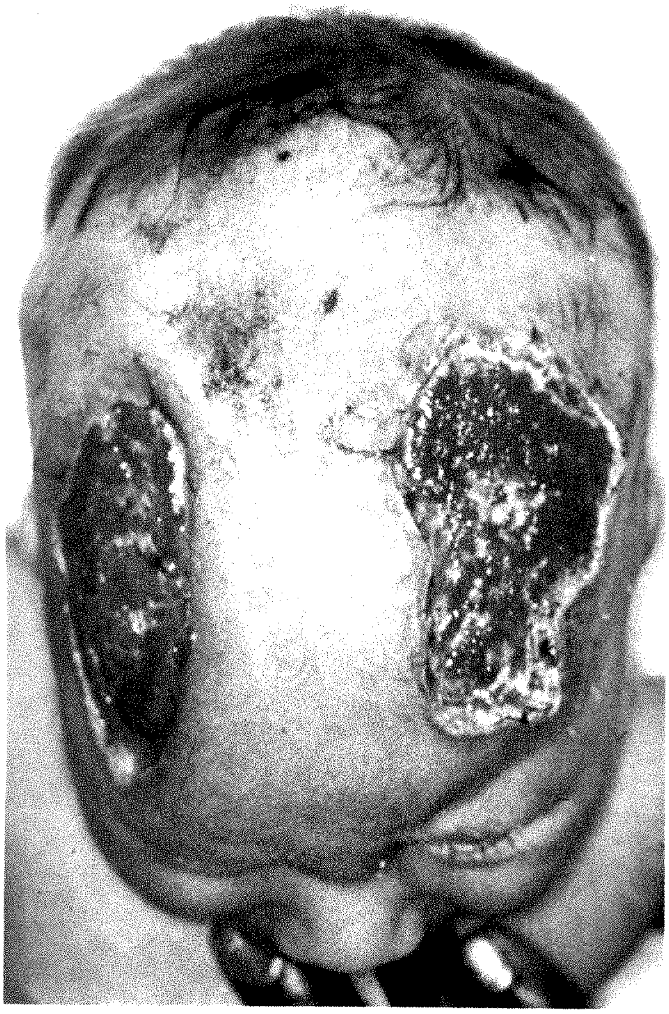

FIG. 5. Newborn infant with full thickness loss of scalp and outer table of the skull from 10% glucose and $CaCl_2$.

Case 8. A 10-year-old girl with Down's Syndrome underwent emergency correction of a Tetrology of Fallot because of severe life threatening hypoxic episodes. During the early postoperative period, intravenous calcium chloride and isoproterenol were administered to sustain adequate cardiac output. Infiltration of the calcium chloride solution into the dorsum of the foot and lower leg caused extensive necrosis (Fig. 7). Necrotic skin and subcutaneous tissue were excised after 10 days. Two days later, extensor tendons and the distal anterior and lateral tibial compartment musculature were obviously necrotic, along with the adjacent periosteum (Fig. 8). Further debridement of necrotic tendons, muscle and bone was done. Subsequently, the orthopedic consultant considered that a functional extremity could not be obtained, and a below-the-knee amputation was done to prevent bacterial seeding of the prosthetic heart patch.

Discussion

Necrosis of skin and underlying soft tissue is an uncommon complication of peripheral intravenous infusions. Skin slough has been previously associated with peripheral noradrenalin infusions and with such cytotoxic drugs as sulfobromophthalein and nitrogen mustard.[3,4] The potential hazards of locally infiltrated solutions containing hypertonic dextrose and calcium are less widely recognized and warrant consideration by those apt to use them.

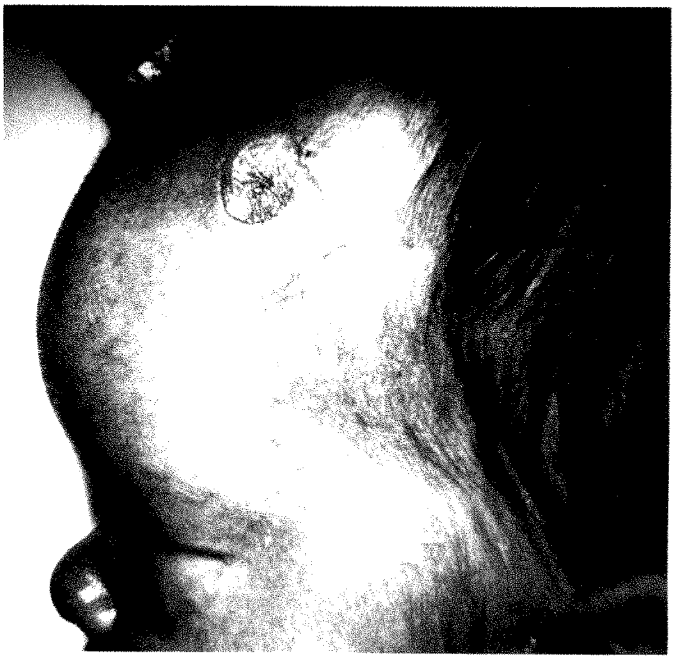

FIG. 6a. Skin necrosis in a premature infant following infiltration of an undiluted solution of calcium gluceptate.

In the 8 cases presented, the extravasated solution leading to tissue slough contained calcium chloride in three instances, calcium gluceptate in one, and a combination of calcium gluceptate and 10% glucose in two. In two cases only 10% glucose was involved.

High concentrations of readily dissociable calcium salts such as calcium chloride precipitate protein and may be directly cytotoxic. If injected or extravasated subcutaneously, calcium chloride causes a painful tissue slough.[1,2] Other clinically employed calcium salts such as calcium

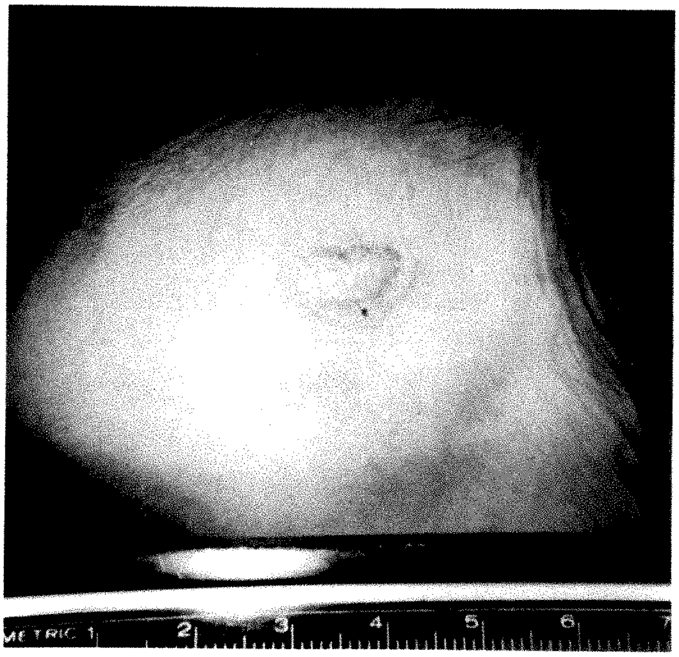

FIG. 6b. Frontal skin healed by scar epithelium.

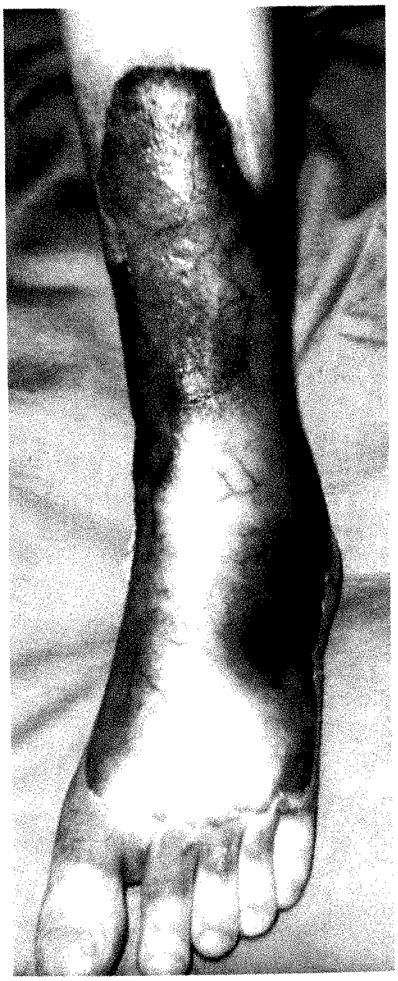

FIG. 7. Extensive necrosis following infiltration of calcium chloride solution.

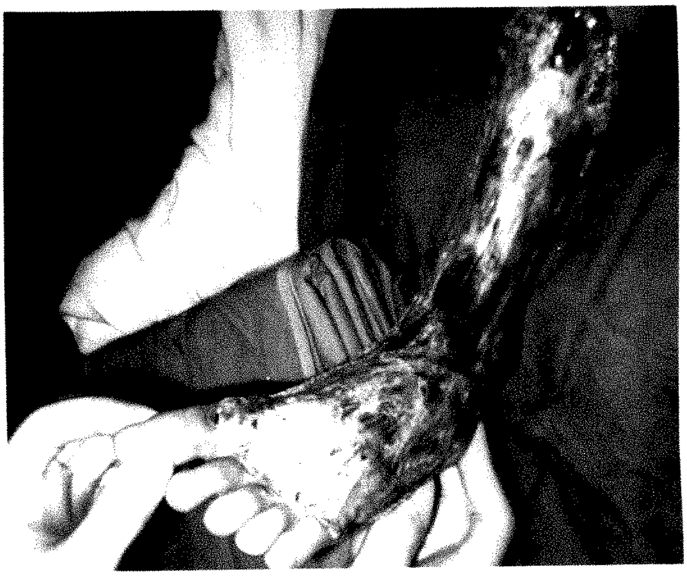

FIG. 8. Appearance of foot two days after primary debridement.

gluconate and calcium gluceptate are much less irritating; but as three of our cases demonstrate, calcium gluceptate can cause tissue necrosis.

The mechanisms by which intravasation of hypertonic glucose solution causes tissue necrosis are not fully understood. Following intravenous infiltration, the fluid is forced by gravity or by an infusion pump into a limited tissue space on the dorsum of a hand, foot or scalp. The hypertonic glucose infiltrate may change interstitial osmotic forces sufficiently to alter the equilibrium between intracellular and extracellular fluid and lead to impaired cell function. This is compounded by pressure within a relatively closed tissue compartment, and the resultant ischemia may initiate a cycle of falling pH, loss of capillary wall integrity, further edema, and eventual cell death.

Treatment of skin and subcutaneous tissue necrosis follows basic plastic surgery principles. The edematous extremity should be splinted and elevated. Devitalized tissue is allowed to demarcate, and then debrided surgically and/or with enzymes. If the wound is small, healing by ingrowth of scar epithelium and contraction can be anticipated. Otherwise, the defect is covered as early as possible with a split thickness skin graft. Reconstructive procedures to improve function or appearance may be undertaken at a later date.

When peripheral infusion of hypertonic glucose or calcium containing solutions is required, precautions should be taken to avoid extravasation. By vigilant monitoring and discontinuance of the infusion at the first sign of infiltration peripheral infusion necrosis can be prevented.

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4. Hanson, D. J.: Intramuscular Injection Injuries and Complications. Gen. Pract., 27:109-15, Jan. 1963.

pHisoHex® between contacts

contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

Protects every hand... the more it's used

Protects every hospital service... the more hands that use it

Unlike many other antibacterial skin cleansers, pHisoHex® creates a bacteriostatic film that reduces resident hand staph and other gram-positive bacteria to minute fractions of original levels after a few days of regular use. Thus, the pHisoHex hand is continuously protected—even between scrubs—through cumulative action when pHisoHex is used as directed. RINSE THOROUGHLY AFTER USE. pHisoHex should not be used on burned or denuded skin. See brief summary for full details of warnings, contraindications, instructions for use, patient selection, and supply.

Gets between staff and staph

pHisoHex®

sudsing antibacterial soapless skin cleanser

pHisoHex contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control. (See Warnings.)

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

pHisoHex SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene. Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only.* If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly with water.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or gastric lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

Winthrop
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New York, N.Y. 10016

(1653)

Upjohn

Anaerobic GI flora–site specific

The gastrointestinal tract of man contains an abundance of microorganisms composed predominantly of anaerobic bacteria. The geographic location of these bacteria in the intestine may explain the different rates of infectious complications associated with injuries to different parts of the gastrointestinal tract. Soilage from the upper portion of the small bowel is usually associated with a lower rate of infection than from the lower small bowel and colon.

Intra-abdominal infections: Intra-abdominal infections may complicate penetrating abdominal wounds, particularly when the integrity of the bowel has been compromised. Such complications are frequently associated with trauma resulting from automobile accidents or criminal violence (such as gunshot wounds or stabbings). Anaerobic infections may occur as postsurgical complications. Peritonitis and abscess formation may cause particular problems. Intra-abdominal infections may also occur when bowel tissue becomes necrotic or nonviable as in cases of vascular compromise, embolic disease, obstruction, strangulation, toxic dilatation, and similar conditions characterized by tissue anoxia.

Appropriate therapy for the infectious complications is often a concern of many physicians.

...and how to manage them: The initiation of antibiotic therapy, particularly when peritonitis exists, may be a matter of immediate importance. In such emergency situations, the surgeon's selection of an antibiotic is frequently made on the basis of scant etiologic evidence. However, his knowledge of the specific normal flora in a given area of the bowel and how the flora can be altered by certain pathologic conditions will aid him greatly in his antibiotic selection.

Therapy which must be initiated presumptively may be chosen discriminatively: While inspection of Gram-stained specimens may prove useful, and cultures from the infection site will eventually provide valuable diagnostic information for the surgeon, the best clue to immediate antibiotic therapy may be the location of the infection. In the normal healthy adult, there is well-defined colonization by specific microorganisms in specific sites of the gastrointestinal tract. Thus a guide to the *normal* inhabitants of various areas may be helpful in suggesting the proper therapeutic agent.

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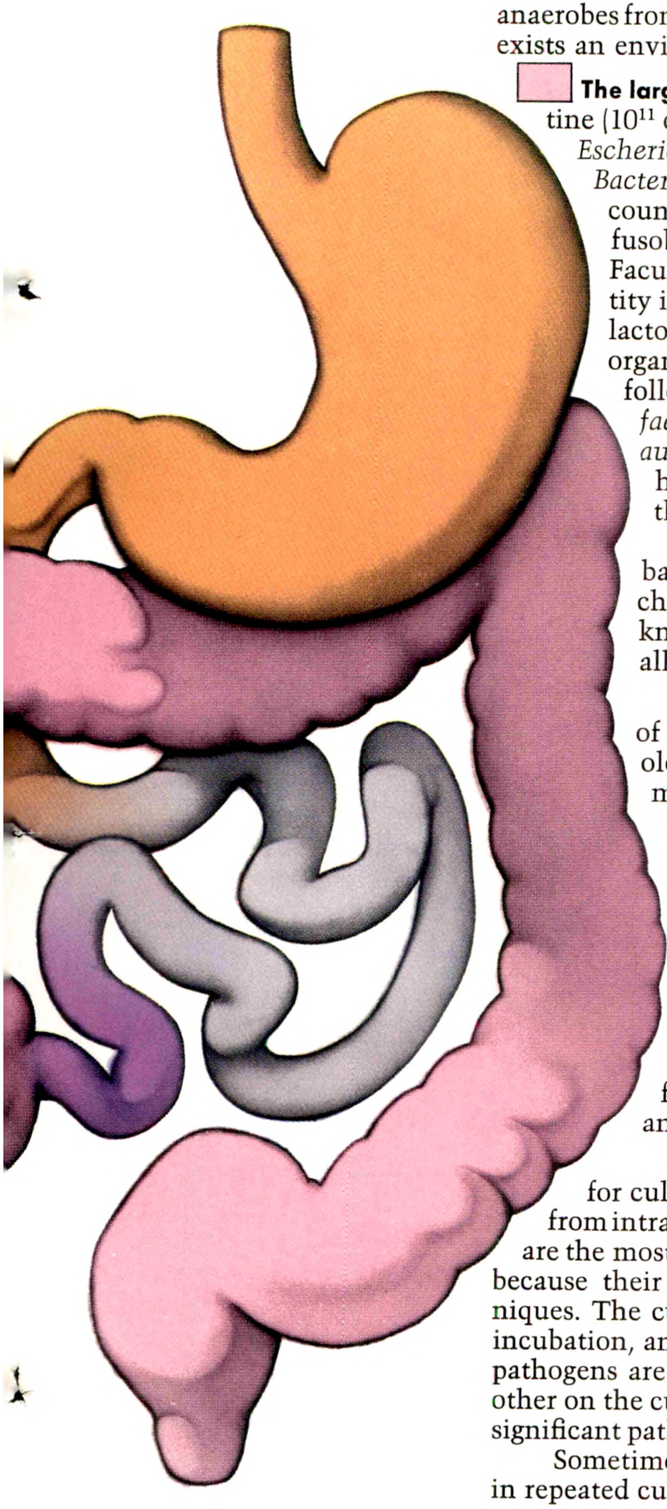
Guide to the normal adult intestinal microflora



🟧 **The stomach, and proximal and middle small bowel:** Here facultative enterococci, lactobacilli and anaerobes (originating in the oral cavity) exist in a concentration of 10^5 or less organisms per ml of contents. *Bacteroides fragilis* is virtually absent. Gastric acidity in this area limits the growth of many bacteria; therefore, most of the organisms are acid-resistant. In the middle portion of the small bowel there is sparse indigenous bacterial colonization, largely because of pronounced motility of this region.

🟪 **The distal small bowel:** In the ileum, enterococci and lactobacilli are seen in approximately the same quantities that occur in the stomach and duodenum. Coliforms are also observed—as are obligate anaerobes. *Bacteroides fragilis* and other fecal anaerobes first appear at this level. In fact, aerobic and anaerobic bacteria exist here in roughly equal proportions. The ileocecal valve, if functioning properly, provides a barrier against colonization by fecal anaerobes from the large bowel into this area. Beyond the ileocecal valve there exists an environment best suited to the proliferation of obligate anaerobes.

🟥 **The large bowel:** Anaerobic microorganisms predominate the large intestine (10^{11} organisms per gram of contents). Obligate anaerobes outnumber *Escherichia coli* 1,000 to 10,000 to one in the large intestine, and *Bacteroides fragilis* is the anaerobic organism most frequently encountered. Other anaerobes, such as peptostreptococci, clostridia, fusobacteria, and eubacteria are also seen although not so profusely. Facultative aerobes are in the decided minority here, but their quantity is no less than elsewhere in the intestinal tract. Enterococci and lactobacilli are each present in concentrations of about 10^6 to 10^8 organisms per gram of contents. *Escherichia coli* is most common, followed by enterococci *(Streptococcus faecalis* and *Streptococcus faecium),* proteus, pseudomonas, and klebsiella. *Staphylococcus aureus* and *Candida albicans* are also present in the large bowel of healthy, normal individuals. The pathogenic potential of each of these microorganisms should never be overlooked.

Because the large bowel contains many different species of bacteria, disease or trauma in this area may present a special challenge. Accordingly, it is important to remember that no known single agent has proved to be uniformly effective against all of these organisms.

Variations in the normal microflora: The normal microflora of the intestinal tract may be substantially altered in certain pathological conditions. These alterations depend upon the patient's medical history and the nature of his present illness. If, for example, the patient has achlorhydria, tissue ischemia, reduced intestinal motility, blind loop syndrome or stasis, or has had previous antibiotic therapy or bowel surgery, significant changes in the microflora of the bowel may be observed. When gastric secretion, intestinal motility or anatomic integrity is altered, the flora of the small bowel may be affected. Under these conditions large numbers of facultative aerobes (e.g., *Escherichia coli)* and obligate anaerobes *(Bacteroides fragilis* and other fecal anaerobes) may be found in this area. A malfunctioning ileocecal valve could permit these aerobic and anaerobic bacteria to colonize the ileum.

Problems in diagnosis: Even though the methods currently used for culturing anaerobes have been greatly improved, bacterial cultures from intra-abdominal sites can be diagnostically misleading. Anaerobes are the most often overlooked category of potentially pathogenic organisms because their detection demands meticulous collection and culture techniques. The cultivation of certain anaerobes may require up to ten days of incubation, and even a brief exposure to air can kill many of them. Multiple pathogens are frequently encountered, and one organism can overgrow another on the culture plate. Blood cultures can be similarly deceptive, since all significant pathogens in a mixed infection are rarely isolated in a single culture.

Sometimes only the consistent reappearance of a given microorganism in repeated cultures is the clue to clinical importance.

Please turn page for information on one antibiotic of significance in the treatment of serious anaerobic intra-abdominal infections.

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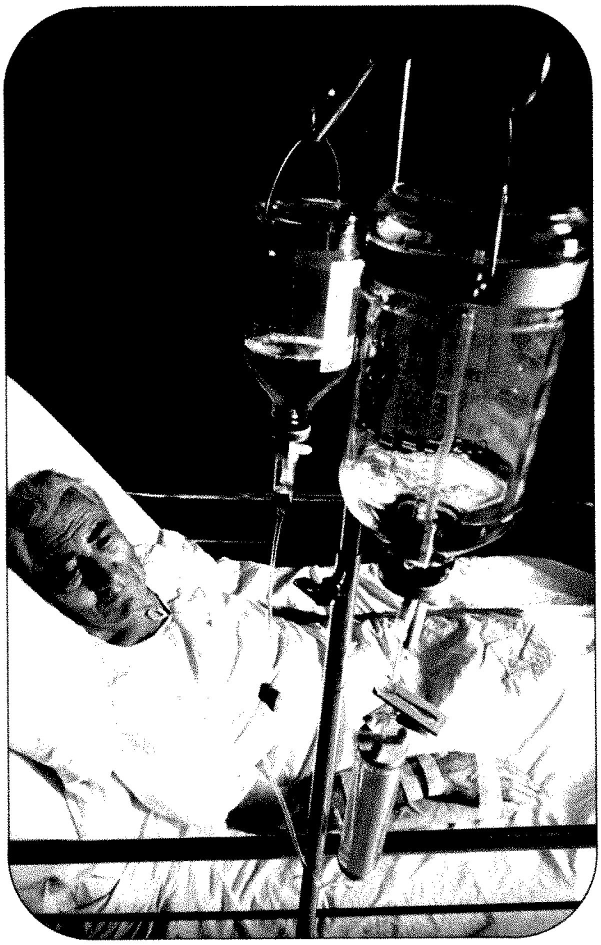
Therapeutic considerations...



Anaerobic activity: Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal-cuff infection caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Effective in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Since it is a parenteral antibiotic, Cleocin PO_4 has been evaluated in serious infections. Its use in these infections should be reserved for penicillin-allergic patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Indications include: serious lower respiratory-tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions.

Other therapeutic considerations:

1. Cleocin PO_4 is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Thus, Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section of the brief summary on the following page.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

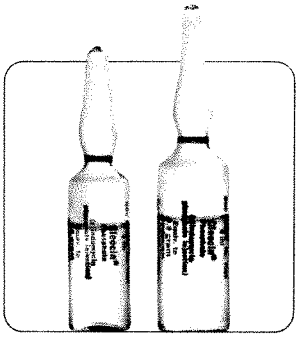
---

*Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g. *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION

...Cleocin® PO4

clindamycin phosphate injection, Upjohn



WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with the close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings:(See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

MED B-4-S (NFM-3) J-4916-9

STERILE SOLUTION

Cleocin PO4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

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Re-live 60 years of action, excitement and great championships in this lavishly illustrated history of the club – and the tournament. With more than 150 photographs, cartoons and illustrations, many in full color. Roll of champions, index, beautiful 8½" x 11½" gift format. At your bookstore or mail coupon today to J. B. LIPPINCOTT COMPANY, P.O. Box 7777-R0400, Philadelphia, Pa. 19175

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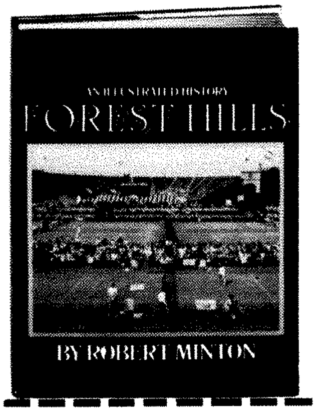

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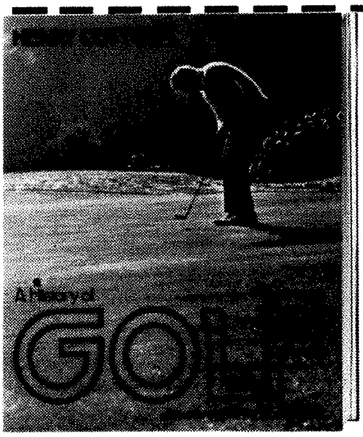

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Follow the world's best players, from "Old" Tom Morris to young Johnny Miller, in this lavish new history by all-time great pro, Henry Cotton. With complete statistics on every major tournament, and more than 150 action photographs – including 30 in full color. "Beautifully illustrated . . . invaluable advice and knowledge."–Sam Snead. At your bookstore or mail the coupon today to J. B. LIPPINCOTT COMPANY, P.O. Box 7777-R0400, Philadelphia, Pa. 19175

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DARVOCET-N® 100

propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

DARVON® COMPOUND-65

propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company, Inc.
Indianapolis, Indiana 46206

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Relief from her postsurgical pain

Darvocet-N® 100

100 mg. propoxyphene napsylate and
650 mg. acetaminophen

contains no aspirin

Darvon®
Compound-65

65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin

for mild to
moderate pain

See summary of prescribing information on adjoining page.

The end of surgery is only the beginning...

When serious infections* complicate recovery

*due to indicated susceptible organisms

'ANCEF' Reported 90% Effective in Serious Bone and Joint Infections

In clinical studies of 30 patients with such infections as septic arthritis and osteomyelitis due to susceptible strains of *Staphylococcus aureus*, 'Ancef' produced good or excellent[†] responses in 90% of the cases.

'ANCEF' Penetrates Infected Bone and Synovial Fluid**

Patient	Tissue/Fluid: Biopsy Specimen	Tissue/Fluid Level (mcg/ml) (Sampling time)	Serum Level (mcg/ml) (Sampling time)	Clinical Response[†]
1	Osteomyelitic Bone	49.4 (1 hour)	30.2 (1 hour)	Good
2	Osteomyelitic Bone	35.6 (5 hours)	26.0 (5 hours)	Excellent
3	Osteomyelitic Bone	22.0 (5 hours)	13.9 (5 hours)	Excellent
4	Synovial Fluid	21 (1 hour) 20 (3 hours) 24 (6 hours)	35 (1 hour) 28 (3 hours) 26 (6 hours)	Good

**(Infections due to susceptible strains of Staph. aureus. Each of the four different patients received 1 gram IM prior to sampling. Therapy was then continued at 1 gram q8h for 13-16 days. Tissue penetration is regarded as essential to therapeutic efficacy but specific antibiotic tissue levels have not been directly correlated with specific therapeutic effects.)

'ANCEF' Offers the Convenience of Both IV and IM Administration

Adverse Reactions

Adverse reactions reported with 'Ancef' include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. Transient rise in SGOT, SGPT, BUN and alkaline phosphate levels has been observed without clinical evidence of renal or hepatic impairment.
For a complete list of adverse reactions with 'Ancef' therapy, please see next page.

Warnings

Cephalosporins should be given cautiously in penicillin-sensitive patients because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.

[†] Excellent response: Initial improvement at 1-3 days with maximum improvement between 3-7 days.
Good response: Initial improvement at 2-4 days with maximum improvement between 4-10 days.

Please see the next page for a brief summary of the prescribing information.

Smith Kline & French Laboratories, Division of SmithKline Corporation

ANCEF®

brand of

STERILE **CEFAZOLIN SODIUM**

Injection: 250 mg, 500 mg and 1 gram vials

meets the challenge, IV or IM

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

meets the challenge, IV or IM

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3- {[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio] methyl} -8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).

Streptococcus pneumoniae (formerly *D. pneumoniae)*
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx, however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible gram-positive cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

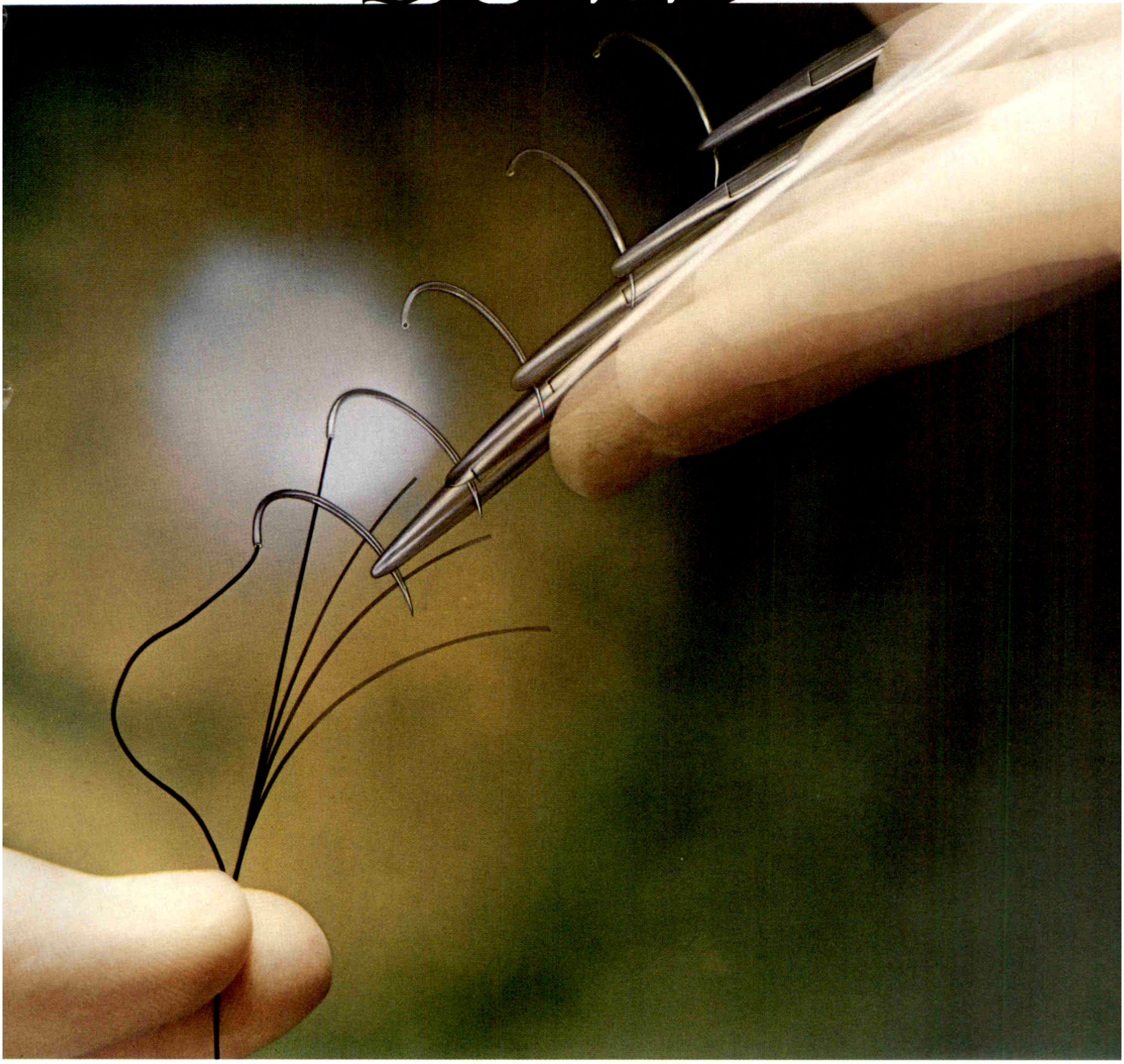
For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, PA 19101

SPEED



Speed is in your hands with
ATRALEASE* control release needled sutures.

Super-Smooth ribbed needle.
Easy to release with no change in technic
for fast interrupted suturing.

ETHICON

*Trademark

The local that gives you the longest anesthesia gives your patient longer postoperative analgesia.

Marcaine® (Brand of bupivacaine hydrochloride) is the local anesthetic that provides the longest duration of action among commonly used local anesthetics. Which minimizes the problems during "continuous" technique or repeat doses.

Marcaine also provides the longer postoperative analgesia. Which reduces the need for postoperative narcotics.

And in data in over 3,000 patients, Marcaine was reported to have excellent or satisfactory results in more than 96% of cases.

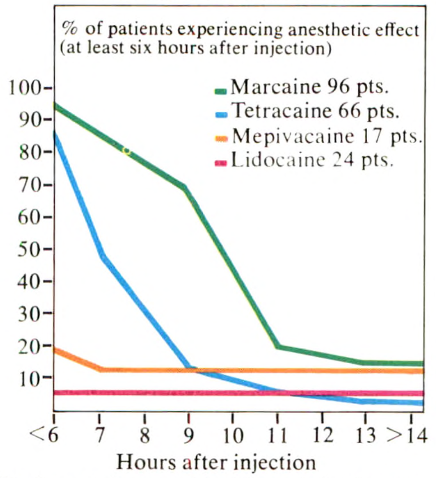
Extended anesthesia for the surgeon

In regional blocks, Marcaine usually provides anesthesia at least 1½ to 2 times longer and occasionally even longer than lidocaine or mepivacaine. And approximately 20% longer than tetracaine. As established in several thousand surgical and obstetrical patients.[1-5]

In fact, a single Marcaine injection may be enough for up to 3½ hours of anesthesia for surgery,[5,6] and often provides analgesia that carries over into the recovery room and beyond.[8] When necessary, doses may be repeated up to once every three hours. Caution is advised in administration of repeat doses to patients with severe liver disease. Until further experience is gained, total daily dose of 400 mg. should not be exceeded nor is administration to children under 12 recommended.

This longer anesthetic action can minimize problems during "continuous" technique or repeat doses. Thus, there is the further advantage of a reduced likelihood of introducing infection since injections are less frequent.

Chart I
Duration of anesthesia
Percentage of patients experiencing anesthetic effect—
Comparison of Marcaine and other local anesthetics*



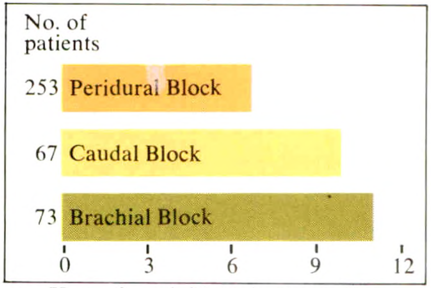
*Equipotent doses used for bilateral, simultaneous blocks of sciatic/femoral, intercostal, or brachial/axillary nerves. Adapted from Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute.

Extended postoperative analgesia for the patient

Marcaine gives your patient more—considerably more—postanesthetic analgesia than other local anesthetics in various types of nerve blocks.[3,5,8,10] An analgesia that persists after the return of sensation. As a result, you may be able to defer,[1,6] and sometimes even eliminate,[6] postoperative narcotics. The table above right illustrates the average duration of time between the initial Marcaine injection and the need for post-op analgesics.

As can be seen in Chart II, many of the 67 patients given Marcaine with epinephrine caudally for rectal surgery did not complain of pain for 12 hours or longer following induction. In another group of 40 patients[10] given Marcaine or mepivacaine locally for tonsillectomy, Marcaine pain relief lasted 3 to 5 times longer than that provided by mepivacaine. And in a study[1] of 84 patients given Marcaine caudally for perineal surgery, complete sensation returned in approximately 8½ hours for the average patient. And the majority of patients did not require a narcotic for an additional 1 to 3 hours.

Chart II
Duration of time between injection of Marcaine and need for postop analgesics†



Hours from initial injection to first hypodermic for pain

†Average—exclusion of extremes and failures. Adapted from Lund, P.C., *et al.*: *Anesth. Analg.* *49*:103, Jan.-Feb. 1970.

Excellent clinical acceptance

Marcaine was administered to 3,112 patients for various types of local anesthesia.[11] Of these patients, only 2 experienced a systemic reaction. Although Marcaine has a very wide safety margin, adverse reactions characteristic of those associated with other amide local anesthetics may occur.

Marcaine is indicated for most anesthetic blocks; however, until further clinical experience is gained, paracervical block is not recommended.

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on next page.

Extends the limits of time in anesthesia [1-5]
Extends the limits of time in postoperative analgesia [3,5,8,10]

Marcaine®

Brand of
bupivacaine hydrochloride

One local does both

Winthrop

MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Actions: Parenteral administration of Marcaine stabilizes the neuronal membrane and prevents initiation and transmission of nerve impulses, thereby effecting local anesthetic action.

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies. The lowest dosage that gives effective anesthesia should be used, to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each repeated dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease. Marcaine (bupivacaine hydrochloride) should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics. Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation. Other causes of reactions to these local anesthetics may be hypersensitivity, idiosyncrasy, or diminished tolerance.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest.

Allergic reactions are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

In obstetrics, cases of fetal bradycardia have occurred.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium, such as ephedrine and metaraminol).

Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate or muscle relaxant, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or a short-acting muscle relaxant (succinylcholine). Intravenous muscle relaxants and barbiturates should only be administered by those familiar with their use.

References: 1. Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine, a review of 2,077 cases, *J.A.M.A. 214*:713, Oct. 26, 1970. **2.** Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine for peripheral nerve block: a comparison with mepivacaine, lidocaine and tetracaine, *Anesthesiology 32*:460, May 1970. **3.** Hollmen, A.: Axillary plexus block: a double-blind study of 59 cases using mepivacaine and LAC-43, *Acta Anaesthesiol. Scand., Suppl. 21*:53, 1966. **4.** Herbring, B. G.: A comparative study of LAC-43, mepivacaine and tetracaine in caudal anesthesia, *Acta Anaesthesiol. Scand., Suppl. 21*:45, 1966. **5.** Bromage, P. R.: A comparison of bupivacaine and tetracaine in epidural anesthesia for surgery, *Can. Anaesth. Soc. J. 16*:37, Jan. 1969. **6.** Lund, P. C., Cwik, J. C., and Vallesteros, F.: Bupivacaine—a new long-acting local anesthetic agent, a preliminary clinical and laboratory report, *Anesth. Analg. 49*:103, Jan.-Feb. 1970. **7.** Ekblom, L. and Widman, B.: A comparison of the properties of LAC-43 prilocaine and mepivacaine in extradural anaesthesia, *Acta Anaesthesiol. Scand., Suppl. 21*:33, 1966. **8.** Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute. **9.** Wise, G. F.: Guest Discussion, *Anesth. Analg. 49*:113, Jan.-Feb. 1970. **10.** Puento-Egido, J. J., Dudeck, J., and Nolte, H.: The clinical use of the local anesthetic agent Marcaine (Carbostesin®), *Anaesthesist 16*:224, August 1967. **11.** Data in the files of the Sterling-Winthrop Research Institute.

Winthrop

Winthrop Laboratories, New York, N.Y. 10016

Extends the limits of time in anesthesia[1-5]
Extends the limits of time in postoperative analgesia[3,5,8,10]

Marcaine®
Brand of
bupivacaine hydrochloride

One local does both

(1664M)

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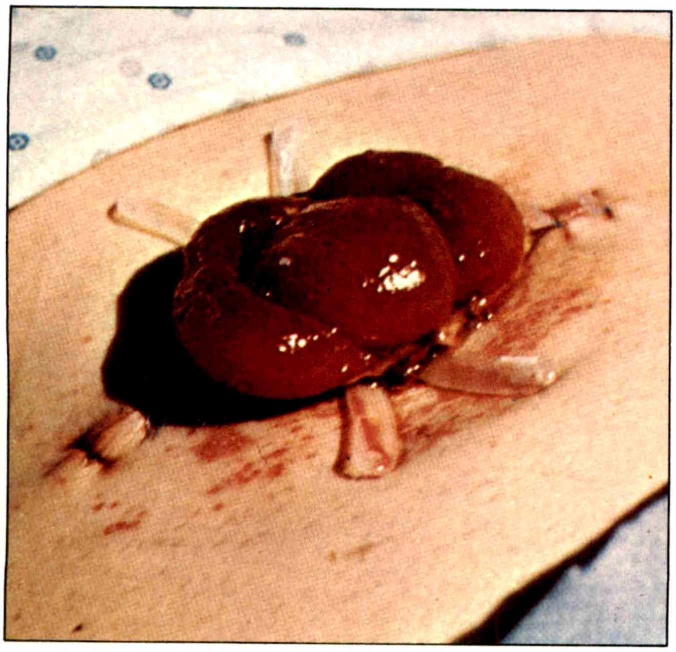

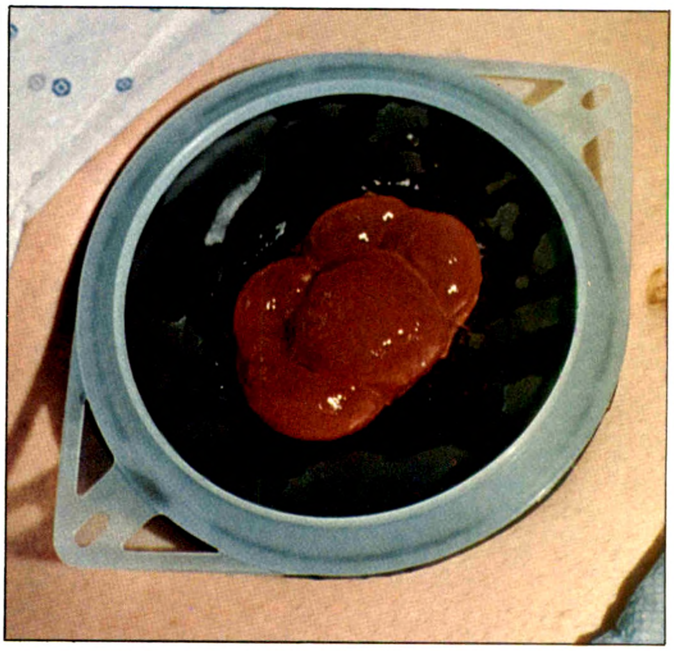

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Corman, Veidenheimer, and Coller[1]
Archives of Surgery, *May, 1974*

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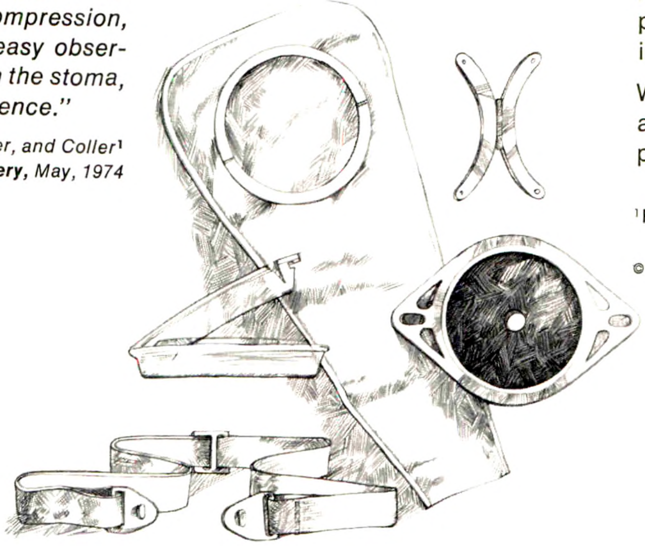

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[1] From the Lahey Clinic Foundation, Boston.

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Intragastric Microbial Colonization in Common Disease States of the Stomach and Duodenum

RONALD LEE NICHOLS, M.D.,[*] JEFFREY W. SMITH, M.S.[†]

Forty-nine patients undergoing elective or emergent gastric surgery have been included in this study. Gastric needle aspiration was performed at the time of surgery in each case, followed by qualitative aerobic and anaerobic bacteriologic analysis. In 18 patients undergoing elective operation for chronic nonobstructing duodenal ulcer a gastric microflora was present in only three patients and no postoperative wound infections were observed. In 29 of 31 patients, in the other groups of patients with bleeding or obstructing duodenal ulcer or in those with gastric ulcer or malignancy, intragastric micro-organisms were present. Six of the 7 postoperative wound infections which developed in these groups of patients were due to one of the same bacteria isolated at the time of original needle aspiration. It appears that the endogenous intragastric microflora is a significant factor in the development of postoperative wound sepsis following gastric resection, in those groups of patients with a compromise of their normal gastric antibacterial inhibitory mechanisms.

THE ASSOCIATION of the intragastric acid-base balance and the bacterial flora of the stomach, duodenum and jejunum was stressed by Arnold[2] as early as 1926. In a series of animal experiments he demonstrated the bacteriostatic action of the gastric acid.[1,2] Subsequent studies by others, employing a variety of sample collection techniques, showed that individuals with normal gastric acid output and motility harbored few if any bacteria in the stomach or proximal intestine.[3,4,6,8] Bacterial overgrowth in the stomach, however, was routinely reported in patients with either decreased gastric acid output (the elderly or patients with pernicious anemia) or altered gastric motility (duodenal or jejunal diverticuli) or both (following peptic ulcer surgery).[9,13,14]

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The organisms that inhabit the stomach in these states enter from the oropharynx by way of saliva or by reflux of proximal intestinal contents through the pylorus. The primary contribution is made by saliva with total aerobes and anaerobes numbering 10^6-10^8 bacteria per ml of saliva. The proximal small bowel contents account for smaller numbers of bacteria, when present, and usually are isolated in concentrations of 10^2-10^3 bacteria per ml of intestinal contents. The common types of aerobes and anaerobes which make up the oral and proximal intestinal microflora are listed in Table 1. In the healthy, colonic anaerobes such as *Bacteroides fragilis* are rarely isolated from proximal intestinal contents.

The purpose of this study was twofold: (1) To examine qualitatively the gastric microflora in patients undergoing elective or emergent gastric operations and (2) To observe whether this gastric microflora, when present, contributed to the postoperative wound infections morbidity. Emphasis was placed on the anaerobic collection and culture techniques.

Materials and Methods

Selection and Preparation of Patients

The study group consisted of 49 patients who were admitted to the West Side Veterans Administration Hospital between July, 1972 and January, 1975. Each patient underwent either elective or emergent gastric surgery. The indications for operation are listed in Table 2. None of the patients received oral or parenteral antibiotics prior to or during surgery. Postoperative antibiotics were

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TABLE 1. *Common Aerobes and Anaerobes Isolated From Saliva and Proximal Intestinal Contents*

Oral Microflora		Proximal Intestinal Microflora	
Aerobes	Streptococci	Aerobes	Escherichia coli
	Staphylococci		Klebsiella species
	Neisseria species		Enterobacter species
	Haemophilus species		Enterococci
Anaerobes	Bacteroides oralis	Anaerobes	Peptostreptococci
	Bacteroides melaninogenicus		Bifidobacteria
	Peptostreptococci		

employed in 4 patients after septic complications were encountered and appropriate specimens collected for culture and sensitivity studies. The average patient age was 54 with an age range of 23 to 81. Cases were included in this study only if they were done during the hours (8:00 a.m. to 6:00 p.m.) that the research microbiologic laboratory was open, thus assuring a rapid, thorough processing of collected samples.

Sample Collection

A needle aspiration of the greater curvature of the stomach using an 18 gauge needle and 50cc syringe was performed on each patient, immediately after entering the peritoneal cavity. Manual pressure on the anterior surface of the stomach was often necessary to assure an adequate sample of gastric contents (2-3 ml). The major portion of each collected gastric aspirate was immediately injected into a sterile anaerobic transport bottle (Anaport).* Care was taken to avoid the transfer of air bubbles into the anaerobic transport vial. Each sterile anaerobic vial contained CO_2, a few drops of a salt solution and an anaerobic indicator dye (resazurin). If the liquid in the vial was pink in color, it indicated oxygen had entered the vial which was then discarded and another transport vial used.

The remainder of each gastric aspirant was left in the original syringe and used for aerobic studies. The anaerobic transport vial and the remainder of each gastric aspirate were taken directly to the research microbiology laboratory where processing was begun within 15 minutes of arrival. Following operation, cultures were obtained from infected sites using similar techniques taking care to collect samples from the deepest area of the wound.

TABLE 2. *Indications for Operation*

Stomach or Duodenal Pathology	Number of Patients
Chronic duodenal ulcer	18
Bleeding duodenal ulcer	12
Obstructing duodenal ulcer	9
Gastric ulcer	6
Gastric carcinoma	4
Total	49

Microbiologic Techniques

Upon arrival in the laboratory, the specimens were immediately passed into an anaerobic glove box.† Once the specimen bottle was in the anaerobic environment, most of the contents was removed with a syringe and needle and plated onto blood agar plates (BAP), blood agar plates with Vitamin K and hemin (BAP-VK) and eosin-methylene blue plates (EMB). A portion was also placed into a tube of chopped meat glucose broth (CMG) for enrichment culturing. Part of the sample was then removed from the anaerobic chamber and inoculated onto EMB and BAP plates. A Gram stain was performed at this point and, if large gram-positive bacilli were seen on the stain, a clostrisel agar plate was inoculated anaerobically with the portion of the specimen remaining in the anaerobic chamber. The aerobic plates were incubated at 35 C in a CO_2 enriched environment and the anaerobic plates were incubated at 35 C in the anaerobic glove box (10% H_2, 10% CO_2, 80% N_2).

After 24 hours, the plates were observed and representatives of all colony types were picked and Gram stained. The aerobic coliforms were identified using the Enterotube system‡ and non-coliform aerobes by using standard bacteriologic techniques. The colonies from the anaerobic incubation also were subcultured onto a BAP plate for capnoic incubation and onto a peptone-yeast glucose extract broth tube (PYG). If the microorganism grew outside of the chamber, it was a facultative organism and was identified using standard aerobic bacteriologic techniques. Those bacteria that did not grow outside the glove box were obligate anaerobes and were identified using the techniques described in the VPI Anaerobe Laboratory Manual.[17] The contents of the PYG broth tube were examined for the presence of metabolic acid and products using gas chromatography and then inoculated into pre-reduced anaerobically sterilized (PRAS) carbohydrate tubes* for identification.[17]

The original petri dishes were observed daily for 7 days and newly appearing colony types were handled as noted above. The CMG tube was subcultured at 48 hours and the colony types cultured were compared to those appearing on the original plates. The culture was kept until all bacterial types observed in the original Gram stain were isolated and identified.

Results

Isolation of intragastric aerobes and/or anaerobes was possible in 32 of the 49 patients undergoing elective or emergent gastric surgery.

The 18 patients who underwent elective operation for

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*Scott Laboratories, Fiskeville, Rhode Island.

†Coy Manufacturing Company, Ann Arbor, Michigan.

‡Roche Diagnostics, Nutley, New Jersey.

TABLE 3. *Microflora of Stomach in Patients With Chronic Non-obstructing Duodenal Ulcer*

No Growth		15
Aerobic Growth		3
Alpha streptococcus, Enterococcus	(1)	
Klebsiella species, Candida species	(1)	
Alpha streptococcus, Neisseria species	(1)	
Anaerobic Growth		0
Mixed (Aerobic-anaerobic) Growth		0
Total Patients		18

chronic non-obstructing duodenal ulcer, all had high preoperative acid levels on the 12 hour overnight study and normal gastric motility as determined by barium study. In this group of patients, the gastric aspirate was sterile in 15 patients (Table 3). The remaining three patients demonstrated purely aerobic growth representative of the endogenous aerobes of the oropharynx and proximal intestine. One patient had a candida species isolated in addition to an aerobic coliform.

The next group of 12 patients included those who underwent emergent surgical procedure for acutely bleeding duodenal ulcer. Acid studies in this group of patients were not done. Results of barium studies showed evidence of intragastric clots in 8 of the 12 patients. The gastric aspirate was bloody in each case and showed growth in all 12 patients (Table 4). One patient had purely aerobic growth while 3 patients had anaerobic growth. The remaining 8 patients had mixed aerobic-anaerobic growth. The isolated anaerobes were, in all cases, the penicillin-sensitive oral type.

Nine patients underwent semi-elective operation for obstructing duodenal ulcer. The overnight gastric acid levels were high in all patients and the barium or gastrografin studies showed the motility disturbance in each case. The gastric aspirate was sterile in one case while the remaining 8 showed growth (Table 5). Five of these patients had purely aerobic growth including a candida species in one case, while one patient had anaerobic growth and two had mixed aerobic/anaerobic growth.

TABLE 4. *Microflora of Stomach in Patients With Bleeding Duodenal Ulcer*

No Growth		0
Aerobic Growth		1
Escherichia coli, Alpha streptococcus Neisseria species	(1)	
Anaerobic Growth		3
Peptostreptococcus	(1)	
Bacteroides oralis, Bacteroides melaninogenicus	(2)	
Mixed (Aerobic-anaerobic) Growth		8
Alpha streptococcus, Bacteroides oralis	(2)	
Escherichia coli, Bacteroides oralis, Peptostreptococcus	(2)	
Alpha streptococcus, Neisseria species, Bacteroides oralis, Bacteroides melaninogenicus	(2)	
Klebsiella species, Bacteroides melaninogenicus	(1)	
Escherichia coli, Klebsiella species, Bifidobacteria	(1)	
Total Patients		12

TABLE 5. *Microflora of Stomach in Patients With Obstructing Duodenal Ulcer*

No Growth		1
Aerobic Growth		5
Candida species	(1)	
Enterobacter species	(2)	
Klebsiella species, Alpha streptococcus	(2)	
Anaerobic Growth		1
Bacteroides oralis, Bacteroides melaninogenicus	(1)	
Mixed (Aerobic-anaerobic) Growth		2
Alpha streptococcus, Bacteroides oralis, Peptostreptococcus	(1)	
Alpha streptococcus, Neisseria species, Bacteroides oralis, Bacteroides melaninogenicus	(1)	
Total Patients		9

Four patients underwent gastric resection for carcinoma of the stomach. The preoperative overnight gastric acid was low in each patient and the barium studies showed motility difficulties (retention of barium) due to the size of each tumor. Gastric aspirate showed a mixed aerobic/anaerobic growth in each of the patients (Table 6). One patient showed growth of *Bacteroides fragilis*, a penicillin-resistant anaerobe, usually found in the distal small bowel and colon.

Five of the 6 patients with gastric ulcer had low preoperative gastric acids. The sixth patient with a prepyloric gastric ulcer had normal levels of acid in the overnight study. This patient had no growth of the gastric aspirate while the others all showed growth (Table 7). One patient had pure aerobic growth while 4 had mixed aerobic/anaerobic growth.

Postoperative wound infection rates are listed in Table 8. The overall wound infection rate was 14%. The group of 18 patients with chronic duodenal ulcer had a sparse gastric microflora at the time of surgery and had no postoperative wound infections. If this group of patients were not included, there were 7 infections in the remaining 31 patients for an overall 22% infection rate. In the

TABLE 6. *Microflora of Stomach in Patients With Carcinoma of Stomach*

No Growth		0
Aerobic Growth		0
Anaerobic Growth		0
Mixed (Aerobic-anaerobic) Growth		4
Klebsiella species, Bacteroides melaninogenicus	(1)	
Alpha streptococcus, Neisseria species, Bacteroides oralis	(1)	
Neisseria species, Escherichia coli, Bacteroides fragilis	(1)	
Alpha streptococcus, Candida species, Bacteroides oralis, Bacteroides melaninogenicus, Peptostreptococcus	(1)	
Total Patients		4

TABLE 7. *Microflora of the Stomach in Patients With Gastric Ulcer*

No Growth		1
Aerobic Growth		1
Klebsiella species, Escherichia coli, Alpha streptococcus		
Anaerobic Growth		0
Mixed (Aerobic-anaerobic) Growth		4
Escherichia coli, Peptostreptococcus	(1)	
Alpha streptococcus, Neisseria species, Bacteroides melaninogenicus	(1)	
Alpha streptococcus, Peptostreptococcus, Bacteroides melaninogenicus	(1)	
Klebsiella species, Alpha streptococcus, Bacteroides oralis	(1)	
Total Patients		6

group of patients undergoing emergent operation for bleeding duodenal ulcer, four of 12 patients developed postoperative wound sepsis (33%).

Six of the 7 wound infections encountered in this series were due to one of the same bacteria isolated from the original gastric needle aspiration.

Two infections were due to aerobic streptococci, two due to aerobic coliforms, while two infections were due to oral anaerobes. In one patient with bleeding duodenal ulcer, wound sepsis was due to *Staphylococcus aureus*, an organism not isolated from the gastric aspirate.

Discussion

The significance and full implications of the gastrointestinal microflora in health and disease continue to remain a mystery. Recent work has appropriately stressed the importance of the endogenous micro-organisms of the lower intestinal tract in the development of post colon resection sepsis.[16,18] Similar attention has not been forthcoming concerning the role of the endogenous microflora of the stomach and proximal intestine in post-surgical sepsis. This fact is probably due to two commonly held misconceptions: (1) that a very low incidence of infections follows all gastric surgery and (2) that the stomach and proximal small intestine harbor few if any bacteria.

Previous reports have stressed the inhibitory effect of gastric acid and normal gastric and intestinal motility on the bacteria in the stomach and proximal intestine.[3,6,10,11] Large concentrations of aerobic and anaerobic microorganisms are delivered in the liter or more of the saliva that enters the stomach daily. Other sources of gastric microflora include the reflux of proximal intestinal contents and ingestion of food stuffs. Drasar et al.[10] showed that ingested bacteria reside only transiently in the normal stomach capable of producing a local pH less than 3.0. Franklin and Skoryna[11] found that bacterial species were isolated routinely from stomachs when the pH was above 2.0. Others[1,3,5,14] have also observed that the pH of gastric juice is intimately associated with both the quality and quantity of the microflora found in the stomach and proximal intestine, although the critical intragastric pH necessary to kill bacteria is somewhat variable, usually being reported between 1-4. Aerobic coliforms are rarely isolated from the normal stomach[9] but are isolated almost uniformly when hypochlorhydria or achlorhydria (pernicious anemia) is present.[13] Frederiksen and colleagues[12] recently reported that significant bacterial counts were usually found in the proximal intestine when the histamine stimulated gastric peak acid outputs were between 0 and 5 mEq H^+ per hour (PAO: 0-5) and rarely found if the PAO was above 15 mEq H^+ per hour. Greenlee et al.[15] however, studied bacterial overgrowth in the jejunum following gastric surgery for chronic duodenal ulcer and found no definite evidence supporting the importance of gastric acid output in controlling bacterial proliferation of the proximal small intestine. Even in the presence of low acid secretion in some of their patients, no bacteria could be isolated while hypersecretion of acid did not always prevent bacterial growth. Other observers[8,12,14] have stressed the importance of the inhibitory effect of normal gastric motility and the mechanical cleansing action of small intestinal peristalsis on the microflora of the stomach and proximal small bowel. Dellipiani and Girdwood[9] isolated intestinal coliforms in the stomachs of greater than 50% of the patients with jejunal diverticuli or in patients with surgically created blind loops such as gastroenterostomies.

TABLE 8. *Postoperative Wound Infections in Patients Undergoing Gastric Surgery*

Indication for Operation	Number of Infections
Chronic duodenal ulcer	0/18-0%
Bleeding duodenal ulcer	4/12-33%
Obstructing duodenal ulcer	1/9 -11%
Gastric ulcer	1/6 -16%
Carcinoma of stomach	1/4 -25%
	7/49-14%

In the present study both gastric acid and normal gastric motility appeared to be important in preventing gastric bacterial colonization. In the group of patients in our study with chronic non-obstructing duodenal ulcer, high acid levels and normal gastric motility was noted preoperatively and few if any gastric bacteria were isolated at the time of surgery. Browning and colleagues[7] have reported on the low incidence of small intestinal colonization in a similar group of unoperated patients.

In the present study we have used direct needle aspiration at the time of operation as our means of specimen collection. This technique has been previously described by Gregan and Hayward[8] and by Bornside and Cohn.[4] Other collection techniques using gastric intubation with a tube or capsule appear less satisfactory for the collection of specimens for anaerobic processing.[14,20] The minimal exposure of the gastric aspirates to the atmospheric environment may account for the higher numbers of anaerobic micro-organisms isolated in this study. Previous studies using nasogastric intubation for specimen collection had found, when present, a predominantly aerobic gastric microflora.[9,11]

It is apparent from this study that gastric bacterial colonization occurs almost uniformly in patients undergoing operation for bleeding or obstructing duodenal ulcer or for gastric ulcer or malignancy (29 of 31 patients). The reason for the gastric colonization in these groups of patients can best be explained by a compromise of the normal inhibitory effects of gastric acid and/or gastric motility. When present, this gastric microflora is usually equally divided between oral or proximal intestinal aerobes and oral penicillin-sensitive anaerobes. Only one penicillin-resistant anaerobe *(Bacteroides fragilis)* was isolated in this study. These same endogenous gastric microorganisms also contributed to wound sepsis in 6 of the 7 patients who developed postoperative infection in this series. The highest infection rate (33%) occurred in the group of patients undergoing emergent surgery for bleeding duodenal ulcer, while the lowest infection rate (0%) occurred in those patients undergoing elective operation for chronic non-obstructing duodenal ulcer.

A study is presently underway to determine if the administration of an appropriate parenteral antibiotic (a cephalosporin or a broad-spectrum penicillin) decreases this infection rate in the high risk groups of patients undergoing gastric surgery. The antibiotic is started preoperatively, so that tissue levels are present at the time of abdominal incision, and is continued for only a 12 hour period thereafter, similar to the approach advocated by Polk[19] in patients undergoing colon resection.

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Studies in Burns:

XIV, Healing in Burn Wounds Treated With Ethyl Linoleate Alone Or in Combination With Selected Topical Antibacterial Agents

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Studies of the efficacy, in terms of burned wound healing, of a mixture of Ethyl Linoleate (ethyl 9-12 (cis, cis) octadecadienoate) with α-1-histidine, α-tocopherol, and TBHQ (hELate) was undertaken in 12 swine. The species was selected so as to study an animal with skin anatomy similar to the human. Statistically significantly greater healing occurred in 730 C/7sec contact burns (20% BSA) treated with hELate than in untreated burns in pigs. Further, there was no contracture noted in the hELate treated lesions, while marked contracture occurred in the untreated burns. Additionally, we noted that there was a proportional increase in weight gain amongst swine studied as their burn lesions epithelialized. In order to evaluate the compatibility of hELate with selected, currently-used topical antibacterial agents, 154 rabbits with 20% 730 C/7 sec contact burns were studied. The lipid was applied (0.01 ml/cm^2 burn) at 1 hour postburning; the topical agent was applied at 2 hours post-burn and every 24-hours. All animals were washed once daily. hELate was applied only once. We found no statistical difference in the number of subjects healed or in the mortality between animals treated with hELate alone and those treated with the agent plus Gentamycin® cream, Neosporin® cream, and silver sulfadiazine 1% in Unibase USP (compounded at Medical College of Georgia specifically and only for this study.) We suggest that Ethyl Linoleate agent (hELate) may be used safely in combination with selected antibacterial substances. Further, these selected combinations seem to be non-toxic and appear to allow the calorie-saving and healing effects of the lipid to proceed unimpeded.

EARLIER, we demonstrated that the naturally-occurring cutaneous lipid, Ethyl Linoleate (ethyl,9-12(cis, cis) octadecadienoate) possessed certain unique properties *vis á vis* burned surfaces. When applied in a single topical dose comprising not more than 0.01 ml/cm^2 burned surface, a highly statistically significant normalization occurred in metabolic heat production. Simultaneously a proportional diminishing and normalization occurred in evaporative water loss from the same surface. Furthermore, re-epithelialization, often with re-growth of hair, occurred over the majority of the treated area in the majority of the subjects treated.[4,5]

In order to establish that the material would be efficacious on a species with skin similar to human, we evaluated the lipid on contact burns in swine.

Additionally, since it was the ultimate aim of our studies to develop a material that could be used in the treatment of human burn injury (and since Ethyl Linoleate is not, in itself, an antibacterial substance), it was necessary to evaluate the compatibility of Ethyl Linoleate with the currently-used topical antibacterial agents. This study of healing and toxicity was conducted in burned rabbits.

Materials and Methods

All experimental burns were contact lesions created by the 7 second application at 83.51±7.38 gm pressure of a pyrex beaker heated to its annealing temperature, 730 C, over a pre-measured 20% of the body surface. The same technician who has been performing this procedure for 10 years in our laboratories created these burn lesions. The Ethyl Linoleate used comprised the 75% pure material to which was added 0.1 mM α-1-histidine, Tertiary Butyl

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Hydroquinone (TBHQ) 5 ppm, and α-tocopherol 5% (w/w). The latter materials have been previously defined as effective antioxidants which prolong the efficacy of the lipid.[3,5] We have named this mixture of Ethyl Linoleate and antioxidants "hĒLate"™®.

The lipid was applied to the burned surface of the animal at one hour after burning. This was the *only* application of hĒLate. In the swine, 0.16±0.06 gm/kg were used (comprising $1.45 \times 10^{-3} \pm 0.53 \times 10^{-4}$ ml/cm²). In the rabbit, a standard dose of 6.68×10^{-3} mg/cm² (0.01 ml/cm²) was applied.

Swine

Twelve Landrace breed swine weighing 19.05±4.70 kg were used in the study. The animals had been clipped, bathed with hexachlorophene-based cleanser, and wormed prior to use. Animals were housed in separate stalls in an outdoor Vivarium, protected only partially from the elements by a roof but no walls. They were fed standard hog feed, and, except for the burning itself were studied unanesthetized. Under pentobarbital anesthesia, a 10% burn was inflicted on each flank of each pig. The total burn was 20%. At random, the right or left side was painted with hĒLate as described. The animals were allowed to waken and were returned to their cages. There was no control of activity, feeding habits, or ambient thermal gradients over the 35-day duration of the study. Animals were weighed at the beginning of the study and at days 7, 11, 14, 21, and 35. They were observed daily with specific regard to the quality of the wounds and evidences of healing. From photographs taken daily, and using a standard diagram, the area re-epithelized was assessed daily.

Rabbits

One hundred fifty-four New Zealand male albino rabbits were employed in the study of the effects of hĒLate used with various other topical agents. Using techniques previously described, a 20% burn lesion was applied to the flanks of each rabbit. Animals were divided into 14 groups. One group, "controls," received as their only therapy a daily bath in Betadine Whirlpool Concentration® (1:8 H_2O). *All* animals, in fact, were washed daily using the solution indicated.

hĒLate was used as the only therapy in one group, and was used in combination with Betadine ointment®, Garramycin cream®, Neosporin cream®, Silvadene cream®, (MCG) silver sulfadiazine cream, Sulfamylon ointment® in one group each. These topical preparations were used alone (without hĒLate) in one group each (Table 3). The (MCG) silver sulfadiazine was compounded at the Medical College of Georgia only for this study and was made up into a 1% w/w preparation using Unibase USP as the vehicle.

TABLE 1. *Percent Healing (X±1SEM) With and Without hĒLate in 730 C/7 sec Contact Burns in Swine*

	% Healed	
Day	hĒLate Treated Side (N=12)**	Non-Treated Side (N=12)
14	17.17±5.28[a]	2.92±1.74
21	30.00±5.96[b]	8.08±4.56
35	89.25±3.78[c]	81.42±4.41†
14	7 of 12 healed > 3% (28.71±4.89)	9/12 healed 0-1%
21	9 of 12 healed > 9% (39.44±4.52)	7/12 healed 0-1%
35	10 of 12 healed > 81% (94.60±1.33) With no contracture	7/12 healed > 81% ($\overline{X}$ and SEM not valid since all had severe contracture)

**h*ĒLate is a mixture of 75% Ethyl Linoleate with α-tocopherol, α-1-histidine and TBHQ. Burns are 7 sec, 730 C 20% BSA contact lesions.

**Treatment comprised one application of 0.16±0.06 gm/kg to the "treated" side at 1 hour post-burn. This was the only treatment. Area treated was 713.99±176.04 cm². Control, untreated area was the contralateral side, and was the same size as the treated area.

†8 of 12 had marked contracture.

With the exception of hĒLate, all other topical agents were applied daily in the manner recommended by the manufacturer and were washed off daily. The application

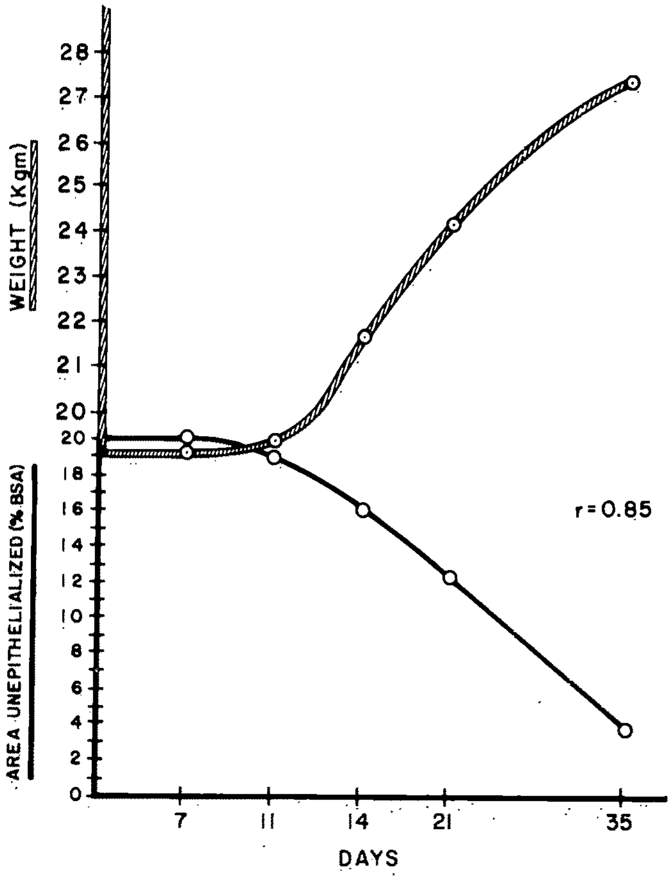

FIG. 1.

TABLE 2. *Lesion Size and Weight Gain Over 35 Days in Burned Swine with 20% Burn, Half of Which Was hĒLate Treated ($\overline{X}$±1SEM)**

	Days					
	0	*7*	*11*	*14*	*21*	*35*
kg Wt	19.05±0.73	19.17±0.86	19.23±0.90	21.63±0.81	23.94±1.29	27.39±0.81
Total Lesion size, T**	20%	20%	19.18±0.50%	15.98±1.25%	12.38±1.78%	2.93±0.73%

*r = 0.85
**T = [20-(0.2xΣ% healed both sides)].

of hĒLate was at—and *only* at—1 hour post-burning. The topical agent was applied at two hours post-burn, and each 24 hours 7 days per week for 21 days. Changes in the wound surface were documented photographically. At death or at 21 days, wounds were debrided and an estimate of healing area was made directly and from the photographs. All animals that died during the period of the study were subjected to necropsy.

Results

Swine

The results of the swine study are summarized in Tables 1 and 2 and Fig. 1. There were no deaths and no manifestations of cutaneous or systemic toxicity in any subject. Those lesions treated with hĒLate demonstrated marked and statistically significantly greater healing over the course of the study than did the non-treated lesions. By day 21, 75% of the treated wounds had healed about 39% of the area burned. At the same time, 58% of the untreated wounds had essentially no manifestion of healing. By the 35th post-burn, post-treatment day, 83% of the treated lesions had healed about 95% of the wound with hair-bearing, non-contracted epithelium. Simultaneously, the untreated areas were severely contracted.

There was little manifestation of healing until the 10-12th day post-burn. Thereafter, healing proceeded in an almost linear fashion (Table 2). Weight gain did not begin to be manifest until the 10-12th day post-burn. Thereafter, it proceeded rapidly (Table 2). There is a significant correlation (r=0.85) between weight gain and total lesion size (Fig. 1).

Rabbits

The results of the rabbit studies are summarized at Tables 3 and 4. In addition, at Table 4 is a X² analysis of

TABLE 3. *Healing and Mortality in Rabbits With 20% BSA Burns Treated With hĒLate and Various Other Topical Antibacterial Agents*

Modality	No. Subjects	*Healing* greater than control, untreated (observed at 21 days postburn)	Died	% Healing ($\overline{X}$±SEM)
Control (no Rx) daily wash	21	4	6	15.7±13.8
hĒLate (h) alone daily wash	55	38	0	76.4±7.7
Betadine® ointment alone and wash	5	1	5	30
Betadine® + h + wash	6	1	4	45
Garramycin® (Gentamycin) cream alone + wash	6	3	0	24.3±3.5
Garramycin® + h + wash	6	2	0	60.0±25
Neosporin® cream alone + wash	6	2	1	32±8
Neosporin® + h + wash	6	4	0	29.5±6.1
Silvadene®* alone + wash	10	3	4	70.0±10
Silvadene® + h + wash	9	0	3	—
Silver Sulfadiazine** alone + wash	6	3	1	66.7±9.7
Silver Sulfadiazine + h + wash	6	5	0	49.0±3.7
Sulfamylon® + wash	6	0	3	—
Sulfamylon® + h + wash	6	1	5	45

*Patented, Marion Laboratories, Kansas City, Mo.
**Compounded at the Medical College of Georgia for this study only. Base is Unibase.
Betadine ointment®: Purdue-Frederick Co., Norwalk, Conn.
Garramycin cream®: Schering Corp., Kenilworth, N.J.
Neosporin cream®: Burroughs-Wellcome & Co., Research Triangle Park, N.C.
Sulfamylon Ointment®: Winthrop Laboratories, New York, N.Y.

TABLE 4. *Summary of Data in Table 3, and X^2 Analysis of the Summarized Data*

	No. Subjects	Healed	Died
A. No Treatment	21	4	6
B. hĒLate-treated, no other Rx	55	38	0
C. Topical antibacterial Rx Rx alone (no hĒLate)	39	12	15
D. hĒLate + Topical* antibacterial Rx	39	13	13

X^2 analysis (df= 1)

Healing		B	C	D
	A	15.39	0.96	1.37
	B		13.46	11.76
	C			0.06

at df= 1,
p>0.05 0.01
X^2= 3.841 6.635

Mortality		B	C	D
	A	17.06	0.59	0.14
	B		25.17	21.28
	C			0.22

*There is *no* statistical difference in number of subjects healed or in mortality between hĒLate alone and hĒLate plus Garramycin cream, Neosporin cream and MCG silver sulfadiazine.

these data. Overall, hĒLate alone produced highly statistically significant healing and was associated with a highly statistically significantly lower mortality (in fact, no deaths in the hĒLate-alone group) than any of the other modalities examined. There were no deaths associated with Garramycin® alone or with hĒLate; Neosporin® cream with hĒLate; or (MCG) silver sulfadiazine with hĒLate. Indeed, there is no statistical difference in the number of subjects healed or in the mortality between animals treated with hĒLate alone and those treated with hĒLate plus Garramycin®, Neosporin® or (MCG) silver sulfadiazine.

The 24 animals that died during therapy with Betadine ointment®, Silvadene Cream® and Sulfamylon ointment® had severe pneumonitis as the chief terminal event. In addition, the animals that died following treatment with Silvadene or Sulfamylon and hĒLate demonstrated focal hepatic necrosis and renal cortical (proximal tubular) necrosis.

The subjects treated with hĒLate plus Betadine ointment, Silvadene, and Sulfamylon appeared ill from about day 3 onward. These animals lost hair from the periorbital areas, lost marked amounts of weight, and were hypersensitive to handling—which apparently produced considerable cutaneous discomfort.

Discussion

It would seem that, under the most adverse conditions and in the most uncontrolled environmental situation, Ethyl Linoleate exerts a salubrious effect on the healing of burn lesions in a skin similar to man's. Even in this highly challenging situation, 75% of the treated lesions in swine healed almost 40% with the re-epithelialization accompanied by some hair re-growth. Simultaneously inflicted, untreated burns on the contralateral sides of these animals showed markedly less propensity to regrowth/epithelium. Sixty-seven per cent of the untreated sides ultimately healed, but in contrast with the treated sides, exhibited marked contracture. In swine, as in our previous studies in rabbits, the Ethyl Linoleate (hĒLate) mixture was applied in small dose only one time post-burn. The agent was the only material used at any time on the pigs' surfaces.

Interestingly enough, in pigs there was a significant correlation (r=0.85) between weight gain and the area re-epithelized (Table 2). Little or no healing was noted through the 11th post-burn/post-treatment day; and through that time, virtually no weight gain had occurred. Subsequently, asymptotic healing and weight gain was noted. The burns were clearly partial thickness by definition, since they healed. It is interesting to speculate on the relationship between healing rate and rate of weight gain. Previously we have deomonstrated that, in a highly controlled environment in a metabolic chamber, there *is* a significant relationship between evaporative water loss and metabolic heat production in rabbits.[4,5] Perhaps, therefore, it is not unreasonable to postulate that in burned swine the same relationship exists.

Zawacki[6] has shown that in partial thickness lesions in guinea pigs, control of the evaporative water loss by the use of xenograft results in re-epithelialization and in protection from weight loss. The mechanism of action of xenograft may be to normalize evaporative water loss—and thereby metabolic heat production. It is, therefore, not unreasonable to speculate that Ethyl Linoleate functions in a similar manner with respect to swine and rabbits.

No toxicity was noted clinically or at autopsy in the hĒLate treated swine. Admittedly, a study of more swine is necessary for a full-blown clinical toxicological study, but the implication is great that in this species, as in rabbits, there is not discernible toxicity.

Clearly, in order to undertake a clinical study of the effects of hĒLate (in terms of reduced calorie demand and, perhaps, burn wound healing,) on the burned human it is insufficient to have shown that hĒLate used alone is non-toxic. hĒLate is not an antibacterial substance.[4] Furthermore, the lipid is applied, for therapeutic purposes, only once, and then in small dose. Since infection of the burn wound is an ever-continuing threat until such time as the wound is "closed," it is presumably essential that some acceptable topical antibacterial agent be used concurrently. Our data indicate that three agents are efficacious when used conjointly with hĒLate and in the manner commonly employed for use of those topical agents. These agents comprise Garramycin® (Gentamycin) cream, Neosporin® cream, and "homemade" silver sulfadiazine in Unibase, USP. There is no statistical difference in the number of burned wounds healed or in the mortality observed in those animals treated with hĒLate alone and those treated with hĒLate plus the topical agents cited (Tables 3 and 4).

There are several possible reasons for the ineffectiveness and/or toxicities observed when the hĒLate-treated subject was concomitantly exposed to Betadine® ointment, Silvadene® or Sulfamylon®. First, it is possible that the lipid obstructed the topical agent's ability to "get at" organisms beneath the surface of the eschar. We have no information that would confirm or deny this possibility. We suspect, by inferred comparison to Garramycin and MCG silver sulfadiazine, that this is not the mechanism: subjects treated with these agents exhibited virtually no toxicity and did, in fact, heal. Since these two agents have some propensity for attacking organisms deep to the surface of the eschar, it is our speculation that the other agents (with the exception of Betadine ointment) had the same opportunity.

It is likely that some interaction occurred between those agents which were ineffective and/or frankly toxic and the hĒLate itself. The mode of death in those 13 animals that died during exposure to Silvadene and Sulfamylon was grossly similar to the deaths we previously observed in mice challenged with a daily dose of Ethyl Linoleate. There was focal hepatic necrosis and necrosis of the proximal renal tubules in these rabbits, and in addition, there was marked interstitial pneumonitis. The deaths that occurred in animals treated with Betadine ointment appeared to be the result of gross contamination of the burned wound and concomitant sepsis. We therefore speculated that the sulfonamide radical interacted in an untoward manner with one or more of the components of the hĒLate mixture. It was our thought, originally, that the interaction occurred between the topical agent and the Ethyl Linoleate itself since the modality of death was so parallel to the hydroperoxide/expoxide mortality observed previously[4,5] and described by others.[1,2]

To test the latter hypothesis, and to test the further hypothesis that the responsible toxic inductor was a component of the vehicle of the Sulfamylon and Silvadene agents, we compounded our own silver sulfadiazine by intermixing equimolar quantities of sodium sulfadiazine and silver nitrate. The resultant material was made up into a 1% cream using Unibase USP as the vehicle. This material performed virtually identically to the hĒLate alone. It produced no deaths—lipid-like, or otherwise—and was associated with healing in 80% of the animals treated.

For a number of reasons, we suspect strongly that the toxic interaction can be traced to one or more materials present in the vehicle into which Sulfamylon and Silvadene are compounded. Studies are underway directed toward defining this hypothesis further. Our current studies indicate, however, that hĒLate may be used concomitantly with Neosporin® and/or Gentamycin® cream among the commercially-available topical antibacterial agents.

Acknowledgments

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Comparative Evaluation of Pancreas Transplantation Techniques

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Three operative techniques for pancreatic transplantation have been compared: pancreaticoduodenal, pancreatic duct-jejunostomy and pancreatic duct-ureterostomy. There were no significant differences in results among these techniques when the autotransplant model was used. The pancreatic duct anastomosis without duodenum probably offers more advantages in the allograft recipient.

PANCREAS TRANSPLANTATION is a laborious operative procedure that involves careful dissection and minimal handling of the pancreas to protect it from ischemic damage and post grafting surface leakage. Several other problems to be faced when selecting an acceptable technique for transplantation are retention of the exocrine function, conservation of the duodenum, or implantation of the main pancreatic duct into the small bowel or the ureter.

Although the technical details of pancreatic transplantation vary considerably between transplant teams,[2–18] there is general evidence to indicate that the exocrine function of the pancreas should always be maintained, to prevent atrophy and fibrosis of the gland. Furthermore, Aquino and co-workers[1] recently demonstrated that the pancreatic duct can be anastomosed directly into the jejunum, thereby eliminating the duodenum during pancreas transplantation. Gliedman, et al.[5] have also shown that the pancreatic duct can be attached to the ureter for pancreatic drainage.

In this paper we compare the most frequently used operative techniques for experimental or clinical pancreas transplantation, namely, pancreaticoduodenal, pancreas without duodenum, and pancreatic duct to ureter anastomosis.

Material and Methods

Adult mongrel dogs of either sex weighing between 17 to 29 kg were anesthetized with sodium methohexital for induction and halothane for maintenance. After endotracheal intubation, they were placed on a positive pressure respirator with room air mixture. All operative procedures were performed under standard aseptic conditions.

Autotransplantation Techniques; *Pancreaticoduodenal Transplant.* Group I (8) dogs underwent an autotransplant procedure (Fig. 1). The proximal pancreas was resected with a portion of the proximal duodenum that was anastomosed to the jejunum in a two-layer fashion. The pancreaticoduodenal artery (PDA) and vein (PV) were anastomosed to the right external iliac artery (REIA) and the right common iliac vein (RCIV), respectively. Gastroenteric continuity was restored with a Billroth I gastroduodenostomy. The bile drainage was restored with a cholecystojejunostomy. This technique is similar to the one described by Ruiz and associates.[15]

Pancreas Transplant without Duodenum; *Pancreatic Duct-Jejunostomy.* Group II (8) dogs underwent a transplantation technique similar to the one described by Aquino and colleagues.[1] Fig. 2 shows that the vascular

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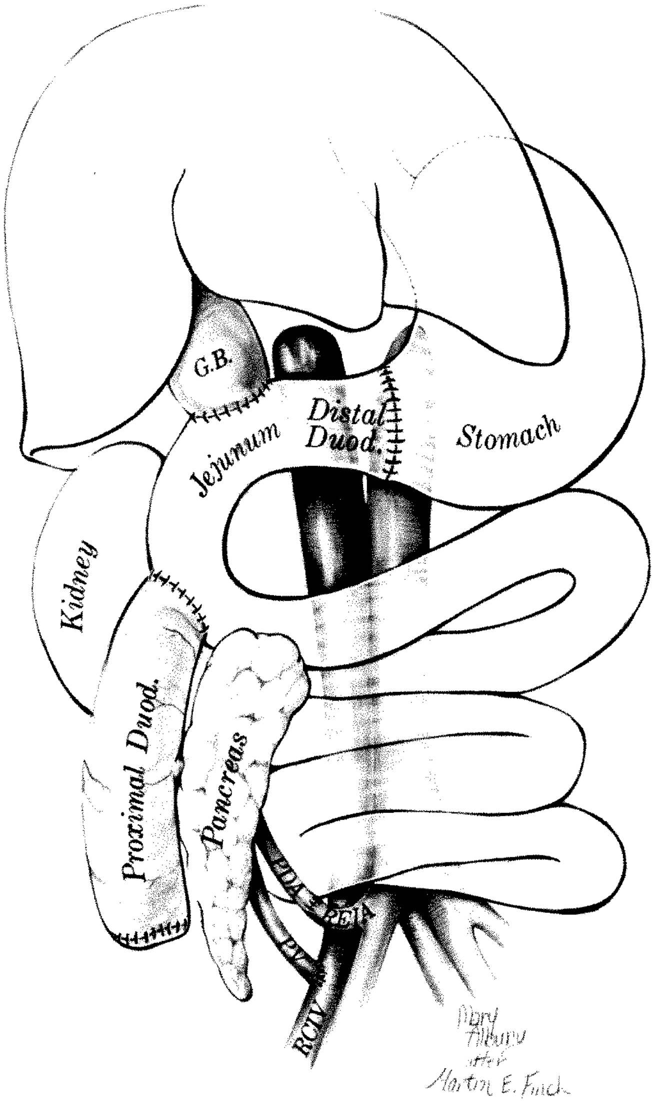

FIG. 1. Technique of pancreaticoduodenal autotransplantation.

supply of the pancreas was maintained by anastomosing the pancreaticoduodenal artery (PDA) to the right external iliac artery (REIA) and the pancreaticoduodenal vein (PV) to the right common iliac vein. The main pancreatic duct was implanted with a periampullary duodenal cuff into the jejunum 20 cm from the cholecystojejunostomy. The gastrointestinal continuity was restored by a Billroth II modified gastrojejunostomy. The biliary drainage was established with a cholecystojejunostomy.

Pancreas Transplant without Duodenum; *Pancreatic Duct-Ureterostomy.* Group III (8) dogs underwent the transplantation technique (Fig. 3) used by Gliedman and colleagues.[5] The proximal pancreas was dissected from the duodenum. A right nephrectomy was performed and the main pancreatic duct was anastomosed to the right distal ureter with 6-0 Tevdek sutures. A polyethylene stent was placed through the pancreatic duct before the duct was anastomosed to the ureter. The vascular supply consisted of pancreaticoduodenal artery-to-right external iliac artery, and pancreaticoduodenal vein-to-right common iliac vein. The gastrointestinal continuity was established by a Billroth II modified gastrojejunostomy, and biliary drainage was restored with a cholecystojejunostomy.

The pancreaticoduodenal or pancreas graft was placed in cold saline (4-6 C) but was not flushed, prior to transplantation. During surgery each dog received 100 ml of Ringer's lactate solution to which 500 mg of methylprednisolone was added. Five hundred milligrams of methylprednisolone was given during the 5 minutes before the vascular clamps were opened, after the transplant was completed. One liter of 10% glucose with half of normal saline and 20 milliequivalents of potassium chloride were given intravenously for 5 days. The amount of fluid given each dog was determined by its state of hydration. One gram of sodium cephalothin was given intravenously

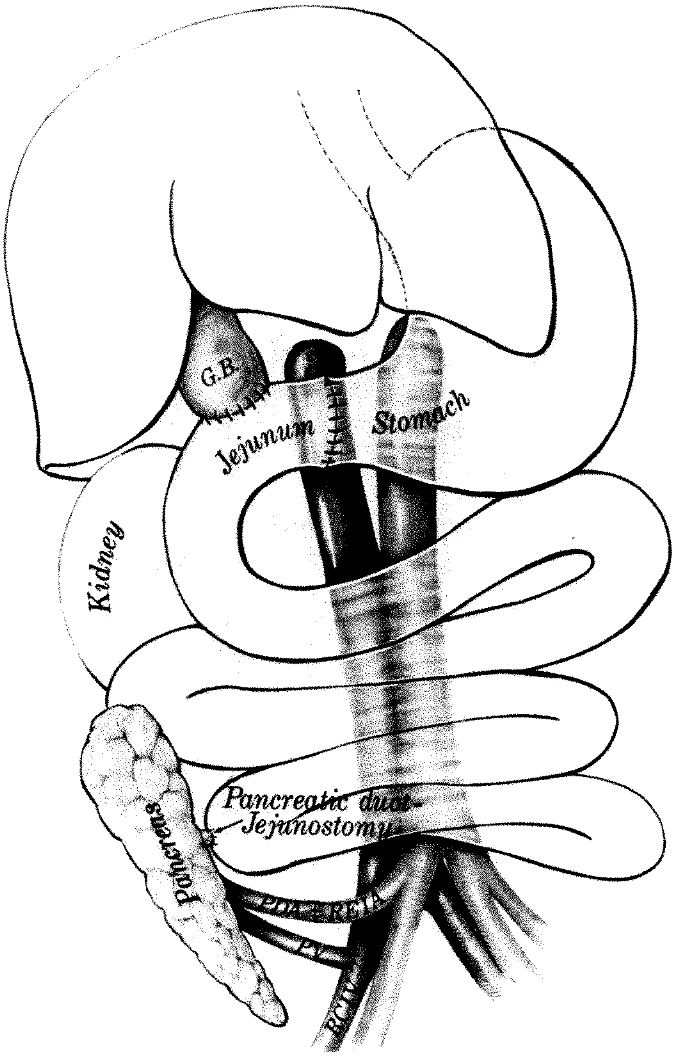

FIG. 2. Technique of pancreas transplant without duodenum; pancreatic duct-jejunostomy.

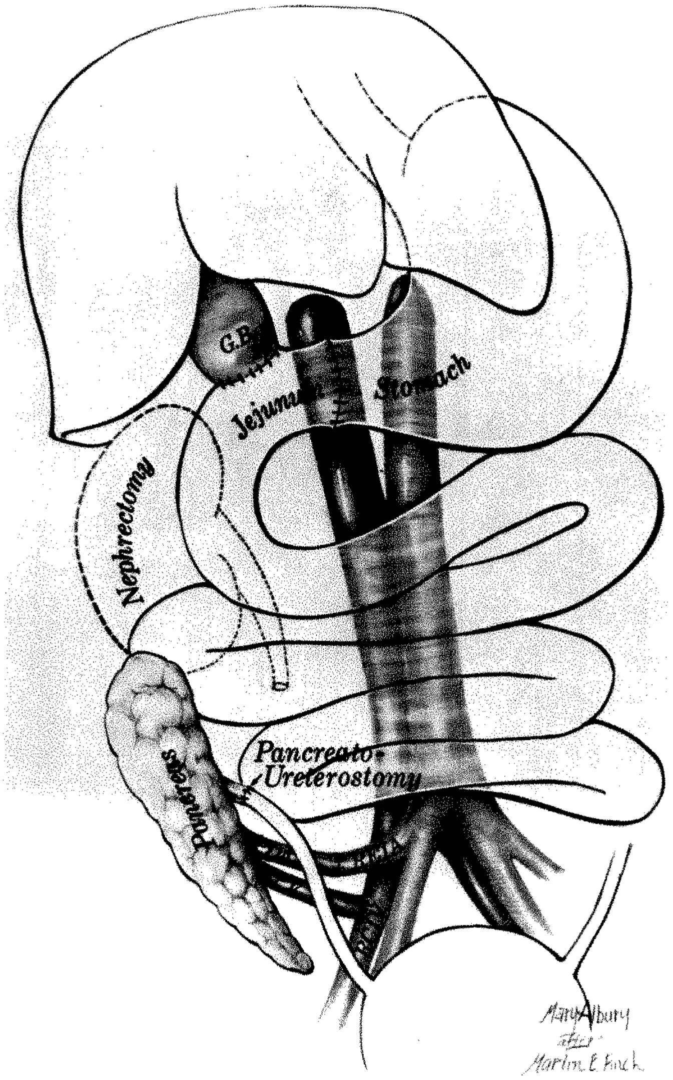

FIG. 3. Technique of pancreas transplant without duodenum, pancreatic duct-ureterostomy.

every 8 hours for the first 4 postoperative days, at which time oral feeding was begun.

All animals were examined daily until death. Complete blood count, serum electrolytes, total proteins, albumin, globulin, blood sugar and serum amylase were determined daily for the first 5 days, then every other day for one week, and once a week thereafter. Glucose tolerance test, tolbutamide stimulation test, 4 day fecal fat specimen and d-xylose absorption test results were recorded twice a month.

Post mortem pancreatic biopsy specimens were taken for final histologic examination.

Results

The causes of death in all groups of dogs are listed in Tables 1, 2 and 3. Mean values ± standard error of the mean were determined in all cases. A statistical analysis was obtained by the Chi square method. All dogs were included in the final analyses.

TABLE 1. *Final Outcome Following Pancreaticoduodenal Transplantation*

Dog #	Survival (days)	Cause of Death	Complications
1	15	Cholecystojejunostomy leak, pneumonia, and intussusception	+
2	6	Portal vein thrombosis	-
3	15	Venous thrombosis	-
4	25	Peritonitis	-
5	30	Pneumonia	-
6	7	Intussusception	-
7	6	Hemorrhagic pancreatitis	-
8	>30	Alive	-

Eight dogs lived longer than 20 days, but the average post-transplant survival was 14 to 16 days. For practical purposes and statistical analysis we chose 30 days as the maximum length of survival, although 4 dogs lived longer than that.

The incidence of postoperative complications and pancreatitis following the three different transplantation techniques were similar (Table 4). The pancreaticoduodenal transplant recipients had no pancreatic duct anastomotic obstruction, but they had the highest incidence of venous thrombosis (25%). There were two instances of pancreatic duct anastomotic obstruction in the pancreas transplantation techniques without duodenum groups. While there was no occurrence of venous thrombosis in the dogs that received a pancreatic duct-jejunostomy, one case occurred in the pancreatic duct-ureterostomy recipients. Pancreatic fistulae did not occur in any of the animals.

TABLE 2. *Final Outcome Following Pancreas Transplantation Without Duodenum (Pancreatic Duct-Jejunostomy).*

Dog #	Survival (days)	Cause of Death	Complications
1	12	Pneumonia	-
2	25	Cachexia	-
3	9	Pancreatitis	-
4	>30	Alive	-
5	8	Pancreatic duct leakage; Pancreatitis	+
6	14	Peritonitis	-
7	>30	Alive	-
8	7	Arterial thrombosis	-

TABLE 3. *Final Outcome Following Pancreas Transplantation Without Duodenum (Pancreatic Duct-Ureterostomy).*

Dog #	Survival (days)	Cause of Death	Complications
1	6	Pancreatic duct leakage; Pancreatitis	+
2	13	Intussusception	-
3	22	Venous thrombosis	-
4	8	Ureteral necrosis	+
5	17	Pneumonia	-
6	>30	Alive	-
7	15	Peritonitis	-
8	7	Pancreatitis	-

The clinical course of all dogs during the first week after surgery was similar. Weight loss, anorexia and dehydration were common, as were diarrheic stools. In addition fecal fat and total fat excretion levels were high during the first three weeks after transplantation, indicating pancreatic exocrine insufficiency.

Hyperamylasemia was present in all dogs within the first postoperative week, with gradual return to preoperative levels. Interestingly, the dogs transplanted with pancreas without duodenum (Groups II and III) had higher amylase values than the pancreaticoduodenal transplant recipients, although the values were not statistically significant. Postoperative serial fasting blood glucose determinations were practically normal in all dogs. Hyperglycemia occurred in one dog in the pancreaticoduodenal transplant group. The dog eventually died from hemorrhagic pancreatitis.

There were no significant differences in hemoglobin, hematocrit, white blood cells, total proteins, albumin, globulin and electrolyte levels among all groups. Also, the glucose tolerance test values were not significantly different. The tolbutamide stimulation test showed low blood glucose levels at 60, 120 and 180 minutes after tolbutamide administration in all dogs, especially in those that survived for several weeks.

No microscopic differences were apparent between any of the transplanted pancreata, and only minimal to moderate hyperemia and edema were observed. Otherwise there were no other important changes except those which caused death, as we have already mentioned.

Discussion

We found no significant post-transplant differences among the three groups of dogs which had either pancreas or pancreaticoduodenal autografts. Pancreatitis appeared to be slightly higher in the pancreas without duodenum recipients and venous thrombosis was higher in the pancreaticoduodenal graft recipients. There was a similar incidence of postoperative complications in all dogs.

Clinical and experimental studies in pancreaticoduodenal allografts frequently have been complicated by rejection of the duodenum before the pancreas demonstrated signs of rejection. Therefore, it was suggested that elimination of the duodenal graft would result in a pancreatic graft with decreased immunological capacity. The resulting operative techniques of pancreas transplantation without duodenum introduced by Aquino and colleagues,[1] and by Gliedman and associates,[5] overcame the potential problems associated with the duodenal segment of the graft. Our study in the autotransplant model confirmed the feasibility of the previous techniques of pancreas transplant without duodenum, and allowed comparison with the pancreaticoduodenal grafts.

The pancreas transplantation without duodenum, pancreatic duct-ureterostomy type, has the advantage of retroperitoneal or extraperitoneal implantation. Also, it is possible to perform a retroperitoneal implantation of the pancreatic duct-jejunostomy if a previous jejunum limb is used for the duct anastomosis before the final transplant procedure, as suggested by Dickerman and colleagues.[4] However, the extensive surgery required for the retroperitoneal approach is a disadvantage. On the other hand, the pancreatic duct-ureterostomy techniques may be responsible for hemorrhagic ureteritis, or cystitis, or even tissue necrosis, because of the high concentrations of amylase draining into the unprotected urinary structures. Gliedman and colleagues[5] have not reported any such complications.

TABLE 4. *Comparative Analysis of Pancreas Transplantation Techniques*

Operation	Average Survival (days)	Long-term Survivors (>30 days)	Postoperative Complications	Pancreatitis as cause of Death	Pancreatic Duct Anastomotic Obstruction	Venous Thrombosis	Pancreatic Fistula
Pancreaticoduodenal	16.0	1/8	1/8	1/8	0/8	2/8	0/8
Pancreatic duct-jejunostomy	16.1	2/8	1/8	2/8	1/8	0/8	0/8
Pancreatic duct-ureterostomy	14.7	1/8	2/8	2/8	1/8	1/8	0/8

Transplantation of the pancreas without duodenum, in any of the two varieties, appears to offer an immunologically more acceptable technique than the original combined pancreaticoduodenal transplant. Therefore, if transplant of the whole pancreas is to be performed the duodenum should not be included. At present, however, it is difficult to determine which procedure, pancreatic duct-jejunostomy or pancreatic duct-ureterostomy, has the best results. The choice of technique must lie with the surgeon's experience with either type of anastomosis, the intraabdominal or extraabdominal position of the pancreas, and in the possible postoperative complications associated with the selected technique. There has been skepticism about the results of the drainage of pancreatic secretions through the urinary tract in the pancreatic duct-ureterostomy technique, but there have been no reports to indicate that this type of hook-up is harmful. The intra-abdominal position of the pancreatic duct-jejunostomy procedure has been given as a partial disadvantage of this technique, however, this position could be converted into an extraperitoneal one by creation of a Roux-en-Y loop.

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Tumor Thickness, Level of Invasion and Node Dissection in Stage I Cutaneous Melanoma

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From a retrospective study of 97 and a prospective study of 41 Stage I cutaneous melanomas, it was found that tumor thickness is a better measure of prognosis than is the level of invasion of the tumor. The chance of developing recurrent disease appears to be directly proportional to tumor thickness. Prophylactic lymph node dissection doubled the rate of survival for patients with lesions greater than 1.50 mm thick but had no effect on those with thinner lesions. Thirty-nine per cent of the patients had lesions less than 0.76 mm thick and all survived free of disease for 5 or more years. Six per cent of the tumors that recurred or metastasized were in an intermediate range of 0.76-1.50 mm thick, and no discriminant could be found to separate these 9 lesions with a bad prognosis from the remaining 18 in this group.

THE ROLE OF PROPHYLACTIC lymph node dissection in the treatment of patients with Stage I cutaneous melanoma is still under debate.[3,4] A probable explanation for the persistence of this debate is the marked heterogeneity of cutaneous melanoma with variation in size, type of lesion and level of invasion, any of which might alter the prognosis and subsequent need for prophylactic node dissection. In 1969 Clark et al.[2] separated melanomas into nodular, superficial spreading and lentigo maligna types and demonstrated that the nodular was the most and the lentigo maligna the least malignant. They also defined four levels of invasion of the dermis and subcutaneous fat and found that prognosis, independent of treatment, was inversely related to the level of invasion. These levels are commonly used to select patients for prophylactic node dissection, restricting such treatment to patients with level III to V lesions. In 1970 we[1] showed that tumor thickness is a reliable measure of prognosis in cutaneous melanoma and this has recently been confirmed by Hansen and McCarten[5] and Wanebo et al.[9] The former group also found that prophylactic node dissection is of value when used for patients with melanomas 1.50 mm or thicker but not for patients with thinner lesions.

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In this study we would like to add a prospective group of 41 patients to our original retrospective series of 97 patients and to compare the usefulness of tumor thickness with Clark's level of invasion in selecting patients for prophylactic lymph node dissection.

Materials and Methods

All patients in this study were free of recurrent or metastatic disease and none had satellite nodules when first seen at the George Washington University Hospital. None of the lesions were of the lentigo malignum type. Their ages ranged from 14 to 79 years (average 39). Twenty were men and 21 women. Seven had lesions of the head and neck; 14 of an extremity; and 20 of the trunk.

Following operation, 17 remained free of disease for 5 or more years, while 24 developed metastatic or recurrent disease. Patients who died of unknown causes, who died in less than 5 years without melanoma and those lost to followup were excluded from the study. Followup was 87% for the prospective group, 92% for the retrospective group and 91% for the combined series. After the publication of our original paper, we discovered that one of the patients with a level IV, 2.50 mm thick lesion had died 5.5 years after surgery, supposedly of a primary bronchogenic carcinoma. Despite repeated attempts, we

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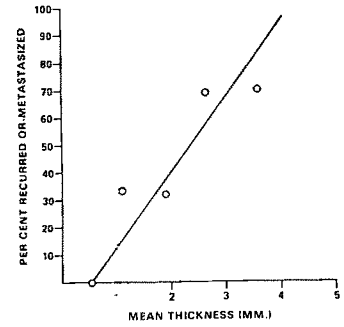

FIG. 1. Percent of patients with recurrent or metastatic disease is plotted against mean tumor thickness of groups from 0-0.75 to 3.01-3.75 mm thick. The correlation coefficient is 0.931 (P = 0.022).

TABLE 1. *Results of Prophylactic Node Dissections Based on Maximal Tumor Thickness. Patients Free of Disease 5+ Years.*

Thickness	LN Dissection	No LN Dissection
<0.76	10/10 (100%)	44/44 (100%)
0.76-1.50	7/10 (70%)	12/17 (70%)
>1.50	14/22 (64%)	11/35 (31%)

Node dissection doubled the survival rate for patients with lesions greater than 1.50 mm thick (P<0.03) but not for those with thinner lesions.

have not been able to obtain the slides from the autopsy and have excluded this case from the study.

The entire lesion was studied if it was small, and several sections were taken through the center of the lesion if it was large. Sections were fixed in neutral formalin, and slides prepared and stained with hematoxylin-eosin in the usual manner.

By means of an ocular micrometer, the maximal thickness of the lesion was measured in several slides from the top of the granular cell layer to the deepest point of invasion. If the lesion was ulcerated, the ulcer base over the deepest point of invasion was used rather than the top of the granular cell layer. The level of invasion was measured by the method of Clark et al.[2]

Results

In Fig. 1, the percentage of cases with recurrent or metastatic disease is plotted against mean tumor thickness for groups of melanomas in a series from 0-0.75 mm to 3.01-3.75 mm. The correlation coefficient is 0.931, which indicates a very strong correlation. This is significant at the 0.022 level.

The distribution of tumor thickness and the clinical results for the combined series are shown in Fig. 2. Most of the therapeutic failures were due to lymph node or hematogenous metastases. Only 4 developed local wound recurrences and 3 of these subsequently died of hematogenous metastases. The fourth is alive and free of disease at 11 years. In 7 cases metastatic tumor was found in clinically negative nodes removed during prophylactic node dissections. The results for the prospective series can be superimposed on the retrospective series. On the basis of tumor thickness, there appears to be three populations of patients with melanoma. The first are those with lesions less than 0.76 mm thick and all have done well. The second is a group of 27 patients with lesions 0.76-1.50 mm thick. Despite the small size of these lesions, 9 developed metastases. Last is a group of 57 patients with lesions thicker than 1.50 mm. As can be seen in Table 1, it is this group that is most likely to benefit from prophylactic lymph node dissection. For this group node dissection doubled the survival rate (P<0.03). By contrast, elective node dissections did not alter the survival rate for patients with lesions less than 1.51 mm thick. Three patients with thick lesions and one with a thin lesion had positive nodes and are free of disease at five or more years. Of the 8 patients with thick lesions who died despite node dissection, 5 had negative nodes. For comparable patients with thin lesions, three had negative nodes.

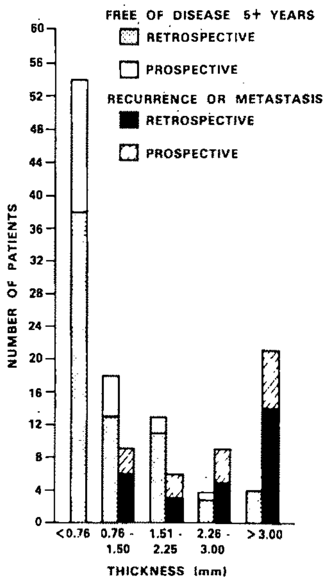

FIG. 2. The distribution of lesions according to tumor thickness. Patients surviving free of disease for 5 or more years are shown in the clear and stippled columns. Those developing recurrent or metastatic diseases are shown in the black and cross-hatched columns. All with lesions less than 0.76 mm thick survived free of disease.

The slides of the nine lesions, 0.76-1.50 mm thick, which metastasized, were compared to those of the 18 that did not. The results are shown in Table 2. The maximal cross-sectional area is the product of the maxi-

TABLE 2. *Analysis of Melanomas 0.76-1.50 mm Thick*

	Free of Disease 5+ Yrs	Recurred or Metastasized
Mean Thickness	1.22	1.01
Mean Maximal Cross-sectional Area	14.0	12.4
Nodular	2	0
Sup. Spread	16	9
Level II	7	2
Level III	7	5
Level IV	4	2
Proph. Node Dissection	6	3
Mitoses/10 HPF	2.4	1.5
Inflammation	Same	Same

No discriminant separated the 9 lesions which recurred or metastasized from the 18 lesions which did not.

TABLE 3. *Clinical Results and Distribution of Lesions According to Clark's[2] Levels of Invasion*

Level	Recurred or Metastasized		
	Retrospective	Prospective	Total
	(97)	(41)	(138)
II	1/39	1/15	4%
III	7/25	5/11	33%
IV	16/27	8/12	61%
V	4/6	3/3	78%

mal thickness and the maximal diameter of the lesion. No discriminant could be found to explain the difference between the two groups.

The data for the levels of invasion are shown in Table 3. The results for the retrospective and prospective series are in reasonably good agreement and, as expected, the rate of recurrence increased as the levels of invasion became deeper.

The distribution of tumor thickness within each of these levels is shown in Table 4. There is great heterogeneity especially within levels III and IV. Of the 14 patients with level III lesions treated with prophylactic node dissection, 11 survived free of disease for 5 or more years (78%) as compared to 15 of the 22 not so treated (68%). For those with level IV lesions the comparable figures are 9 of 17 for the treated group (53%) and 8 of 22 for those not treated (36%). The difference between the treated and untreated groups are not statistically significant. No patients with level V lesions were treated with prophylactic node dissections. For level II lesions survival was over 90% for both treatment groups.

Discussion

Tumor thickness and level of invasion of cutaneous melanoma are independent variables which are relatively congruent in levels II and V but not in levels III and IV. Though most level II lesions are thin and all level V lesions are thick, there is great variation in thickness for levels III and IV and this has recently been confirmed by others.[5,9] Since the chance of developing recurrent disease appears to be directly proportional to tumor thickness and the mean survival following surgery appears to be inversely proportional to tumor thickness,[5] this heterogeneity within levels III and IV is a serious defect if the level of invasion is to be used to guide treatment. If the suggestion that all patients with level III to V melanomas should be treated with elective node dissection is followed, and if our patient population is not unique, the following can be expected:

1. Seventeen per cent of patients with level II lesions will not be treated with node dissection but will have lesions 0.76-1.50 mm thick. Though this is in the range for which the value of elective node dissection is still to be proven, one such patient had positive nodes and is alive and free of disease at more than 5 years.
2. Twenty-five per cent of patients with level III lesions will have unnecessary node dissections with lesions less than 0.76 mm thick. We have yet to see such a lesion recur or metastasize.
3. If one wishes to limit node dissections to patients with lesions greater than 1.50 mm thick, for whom node dissections are of proven value, 29% of patients with level III to V lesions will be treated unnecessarily.

Another serious problem in using Clark's levels of invasion is the difficulty in differentiating between an advanced level II and a level III lesion. The difference is somewhat subjective, and several pathologists have commented on this problem.[7,8,9] In one collaborative study,[8] agreement among the pathologists could only be achieved after instruction by Dr. Clark. By contrast, measurement of tumor thickness is objective, and good agreement among pathologists is to be expected.

TABLE 4. *Distribution of Tumor Thickness For Each of Clark's Levels of Invasion*[2]

Level		Free of Disease 5 Yrs	Recurred or Metastasized
II	<0.76	45 (7)*	0
	0.76-1.50	7 (3)	2 (1)
III	<0.76	9 (3)	0
	0.76-1.50	7	5 (3) [1]†
	1.51-2.25	4 (3)	1
	2.26-3.00	3 (2)	4 (1)
	>3.00	1 (1)	2 (1) [1]
IV	<0.76	0	0
	0.76-1.50	4 (2)	2
	1.51-2.25	9 (3)	5 (3) [1]
	2.26-3.00	0	6 (1)
	>3.00	2 (2)	11 (6) [4]
V	2.26-3.00	1	0
	>3.00	1	7

*Number treated with prophylactic node dissection.

†Number with positive nodes in prophylactic dissection.

There is great heterogeneity within each group, especially in levels III and IV. The number of patients treated with prophylactic node dissection is indicated in parentheses. The number of patients with positive nodes in prophylactic dissections is shown in brackets.

For these reasons, we believe that tumor thickness rather than the level of invasion should be used to select patients for prophylactic node dissection. It is clear that patients with lesions less than 0.76 mm thick should not be subjected to node dissection while those with lesions greater than 1.50 mm should be so treated. The indications for node dissection for the group with lesions 0.76-1.50 mm thick are still obscure and the treatment will continue to depend on the intuition of the surgeon, perhaps influenced by the distance between the lesion and the nearest group of lymph nodes. We are aware of the hazards of using data from retrospective non-randomized studies to guide therapy, but this is all we have at the present time. Clearly a cooperative prospective study of randomized patients is needed to prove the value of prophylactic node dissection in cutaneous melanoma. From the data at hand, this study should be limited to patients with lesions thicker than 0.75 mm.

In a retrospective study of 151 melanomas at Memorial-Sloan Kettering Cancer Center, Wanebo et al.[9] found three melanomas less than 0.76 mm which metastasized. Two were subungual lesions, which are uncommon and were not encountered in our study. One was a cutaneous level II lesion 0.60 mm thick. In a review of all primary cutaneous melanomas at the National Cancer Institute in 1969, we found one lethal level II lesion 0.45 mm thick. Very thin lethal cutaneous melanomas are very rare and are most likely to be seen at very large referral centers.

Hansen and McCarten,[5] in a retrospective study of 154 melanomas (50 of head and neck, 36 of trunk and 68 of extremities), also found tumor thickness to be of greater value than level of invasion in selecting patients for prophylactic node dissection. They report that prophylactic lymph node dissection is of value for melanomas 1.50 mm or thicker but not for thinner lesions. Seventy-seven per cent of treated patients survived free of disease for an average of 8 years as compared to 43% for the untreated group ($P<0.01$). Though their overall study included patients with lentigo maligna melanoma, a group we excluded because of its low degree of malignancy, none of the patients in their treated group of thick melanomas had such a lesion.[6]

They only encountered one lethal melanoma less than 1.50 mm thick, while we found 9. This may reflect differences in the rates at which rural Canadians and urban white Washingtonians seek medical care. The more lethal thin melanomas may have metastasized before the patients saw the physicians, thus excluding these patients from the stage I group under study.

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In Situ Preservation of Cadaver Kidneys for Transplantation:

Laboratory Observations and Clinical Application

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Many kidneys obtained from cadaver donors undergoing sudden cardiac arrest cannot be transplanted due to the long periods of warm ischemia from the moment of arrest to nephrectomy. A double-balloon-triple-lumen catheter for the rapid *in situ* preservation of cadaver kidneys has been designed. Used in combination with equipment routinely found in any hospital, it can cool human kidneys in situ to 10-15 C and maintain this temperature until nephrectomy can be performed. Kidneys preserved with this catheter have functioned after transplantation into suitable recipients. This report describes the design and laboratory evaluation of this new device, its clinical effectiveness and technique of insertion.

From the Baylor College of Medicine, Houston, Texas

BECAUSE of the insufficient number of kidneys available for homotransplantation, it is necessary to use every available renal graft. Kidneys from living donors or from cadaver donors who fulfill the criteria for cerebral death[3] have been used with variable success.[7]

Accident victims who sustain severe head trauma often exhibit clinical signs of neurologic death but these patients' unstable cardiovascular system causes such potential donors to succumb in less than 24 hours after arrival at the emergency center. Since many transplantation committees require two isoelectric electroencephalograms (EEG) 24 hours apart to be able to use the patient as a "beating heart donor," many of these potential donors cannot be used.

Nephrectomy in these patients can be performed after cardiac arrest. However, the long periods of warm ischemia between cardiac arrest and nephrectomy would render the organ nonfunctional after transplantation into a recipient.

To determine whether human kidneys obtained after cessation of cardiac action would function after transplantation, we performed nephrectomy in 10 donors. Ninety per cent of the organs we harvested in this fashion had poor perfusion characteristics due to prolonged warm ischemia and had to be discarded.[6] It became apparent that a method of rapid *in situ* cooling to 10-15 C was

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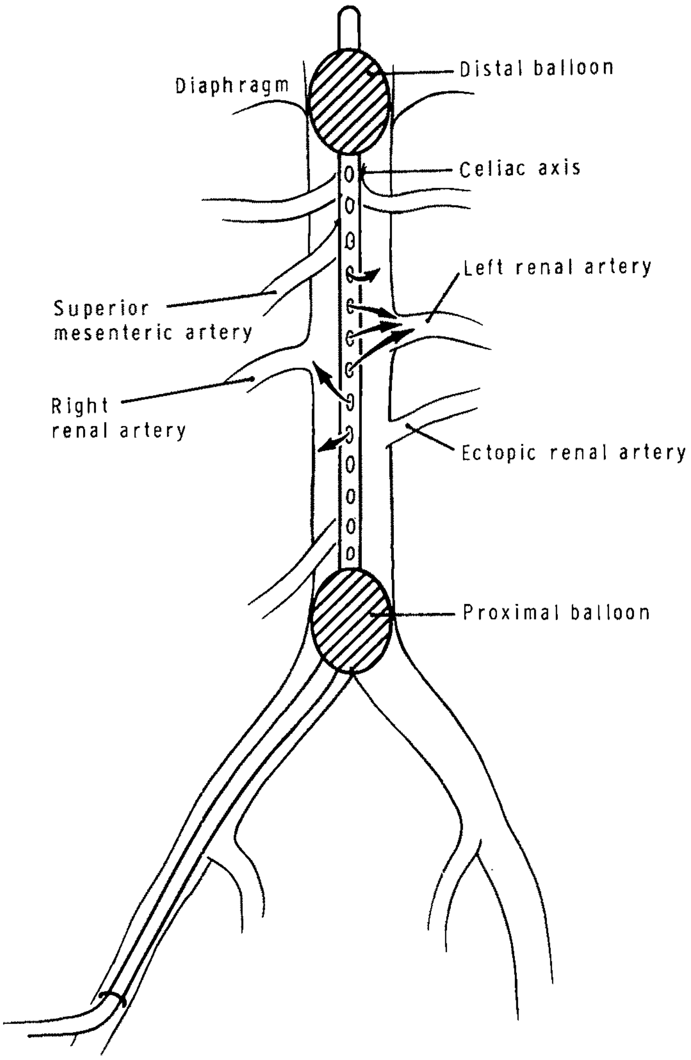


FIG. 1. Diagramatic representation of the double-balloon-triple-lumen catheter when inserted into the abdominal aorta.

necessary to preserve human kidneys. At 10-15 C the metabolic needs of the kidneys are significantly reduced and renal function is preserved as demonstrated by Levy.[8]

Banowsky had cooled canine kidneys *in situ* by the infusion of a chilled solution delivered to the renal arteries via a catheter placed in the abdominal aorta. These kidneys functioned after transplantation into other dogs.[1] However, this technique required fluoroscopy for proper placement. Ectopic renal vessels could not be predictably infused.

We have designed a catheter, The Double-Balloon-Triple-Lumen Catheter* (DBTL), which allows the rapid *in situ* preservation of human kidneys without the use of sophisticated equipment. The purpose of this report is to describe the design and laboratory evaluation of this new device and to describe the clinical effectiveness of this catheter.

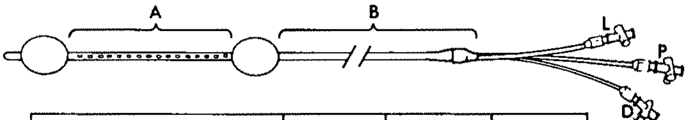
MATERIALS AND METHODS

Catheter Design: In order to determine proper design of such a device, we performed one hundred cadaver dissections to study the anatomic relationship of the renal arteries to the abdominal aorta. We measured the distance from the bifurcation of the aorta to the diaphragm, the distance between the right and left renal arteries, the distance from the highest renal artery to the diaphragm and the distance from the lowest renal artery to the bifurcation of the aorta.

We used these measurements to design a double-balloon-triple-lumen catheter. The balloons, located in the abdominal aorta at the bifurcation and at the level of the diaphragm, block the aorta and confine the infusion to the area between the bifurcation and the diaphragm. Multiple openings in the segments between the balloons allow simultaneous infusion of both renal arteries and any ectopic renal vessels (Fig. 1).

We found that measurements were age dependent so we designed three different catheters: one for adults,* another for donors in the 11-15 year age group† and the third for the 4-10 year age group‡ (Fig. 2). After the prototypes were built, they were tested for size in cadavers. For the three groups of potential donors, we found the position of the balloons, catheter diameter and occlusive potential of the balloons were as predicted.

In order to build a prototype to use for experimental studies, similar measurements were taken in 10 dogs weighing between 18-23 kg. Coincidentally, the catheter designed for humans in the 11-15 year age group fits a dog



	Adult	11-15 years	4-10 years
Size	15 1/2 Fr	11.5 Fr	10.5 Fr
Length of balloons	3.0 cm	3.0 cm	3.0 cm
Distance "A"	10.0 cm	7.5 cm	5.0 cm
Distance "B"	48.0 cm	50.5 cm	43.0 cm
Total length	65.0 cm	65.0 cm	55.0 cm
Balloon inflation lumen (I. D.)	.066 cm	.046 cm	.046 cm
Perfusion lumen (I. D.)	.210 cm	.141 cm	.115 cm

FIG. 2. Catheter sizes available for human use: L = Infusion lumen; P = Proximal or "bifurcation" balloon; D = Distal or "diaphragmatic" balloon.

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*Garcia-Lefrak Catheter, U.S. Catheter and Instrument Corporation, Glenn Falls, New York 12801.

*Garcia-Lefrak Catheter, U.S. Catheter and Instrument Corporation 5266 (a).

†Garcia-Lefrak Catheter, U.S. Catheter and Instrument Corporation 5266 (b).

‡Garcia-Lefrak Catheter, U.S. Catheter and Instrument Corporation 5266 (c).

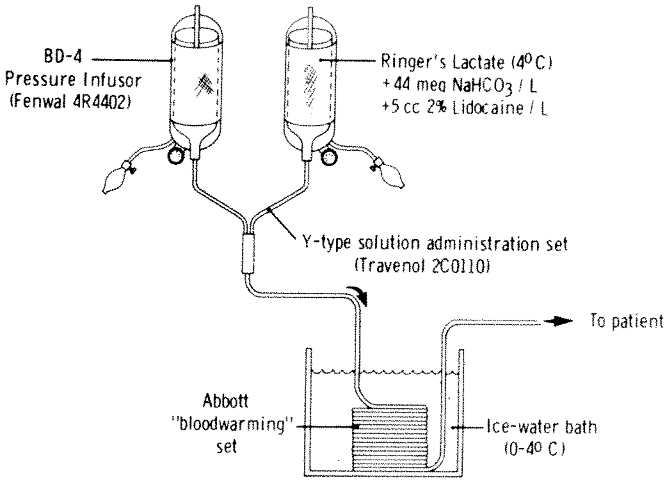

FIG. 3. Infusion setup for the double-balloon-triple-lumen catheter.

in this weight range and was used for the experimental studies.

Infusion Setup and Infusate Composition: As the infusate, we used lactated Ringer's Solution to which we added 44 meq Na HCO_3/l and 5 ml of 2% lidocaine/l. The infusate is stored at 4 C in plastic bags. Two bags of infusate are connected by using a "Y-type IV Infusion Setup."®* On the exterior of each bag, a B-4 "Pressure Infusor"®† is applied.

Plastic tubing, as commonly used for intravenous fluid administration, is then connected to a "Blood Warming Coil"®‡ immersed in an ice water bucket to maintain the temperature of the infusate at 4 C. The coil is connected to the DBTL Catheter, and the infusion fluid is administered to the donor or experimental animal through the catheter (Fig. 3).

Method of Insertion: We inserted the catheter into the abdominal aorta through a left femoral artery cutdown in both humans and experimental animals. We then used a "pull-back technique" to position the balloons: the catheter is inserted as far as it can go and the lower balloon (P), inflated with 5-20 ml of sterile normal saline then the catheter is pulled back to the aortic bifurcation. When inflated, this balloon is too large to fit inside the iliac arteries, so it remains at the aortic bifurcation.

The distal or diaphragmatic balloon (D) is then inflated with 10-20 ml of sterile saline. With the catheter in this position and both balloons occluding the aorta, infusion is started.

A size 16 Fr suction catheter must be introduced into the inferior vena cava through the left femoral vein at the time of insertion of the DBTL Catheter to drain blood and infusate from the donor or experimental animal.

Experimental Studies: Mongrel dogs, weighing 18-23 kg were anesthetized with an intramuscular injection of sodium pentobarbital (30 mg/kg), then connected to an electrocardiographic monitor. Blood pressure was monitored in the right femoral artery with a polyethylene catheter connected to a strain gauge transducer.

The kidneys were exposed using a midline abdominal incision. We monitored their temperature with a needle thermocouple device inserted 0.5 cm into the renal parenchyma. Rectal temperature was continuously probe monitored.

Once the catheter had been positioned we ascertained the position of the balloons by palpating the abdominal

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EXPERIMENTAL GROUPS

Group #	Foley Catheter in Aorta	Double Balloon Triple Lumen Catheter	Interior Vena Cava Catheter	Phenoxybenzamine (1 mg/kg) Administration			Phentolamine (0.5 mg/kg) Administration		
				60 min. before	5 min. before	Through Catheter	60 min. before	5 min. before	Through Catheter
I (Control)	+	0	0	+	0	0	0	0	0
II	0	+	+	0	0	0	0	0	0
III	0	+	0	+	0	0	0	0	0
IV	0	+	+	+	0	0	0	0	0
V	0	+	+	0	+	0	0	0	0
VI	0	+	+	0	0	+	0	0	0
VII	0	+	+	0	0	0	+	0	0
VIII	0	+	+	0	0	0	0	+	0
IX	0	+	+	0	0	0	0	0	+

TABLE 1. One hour before induction of ventricular fibrillation all animals were given: 6.0 gm Mannitol, 100 mg. Solu Medrol, and 1 mg/kg Heparin.

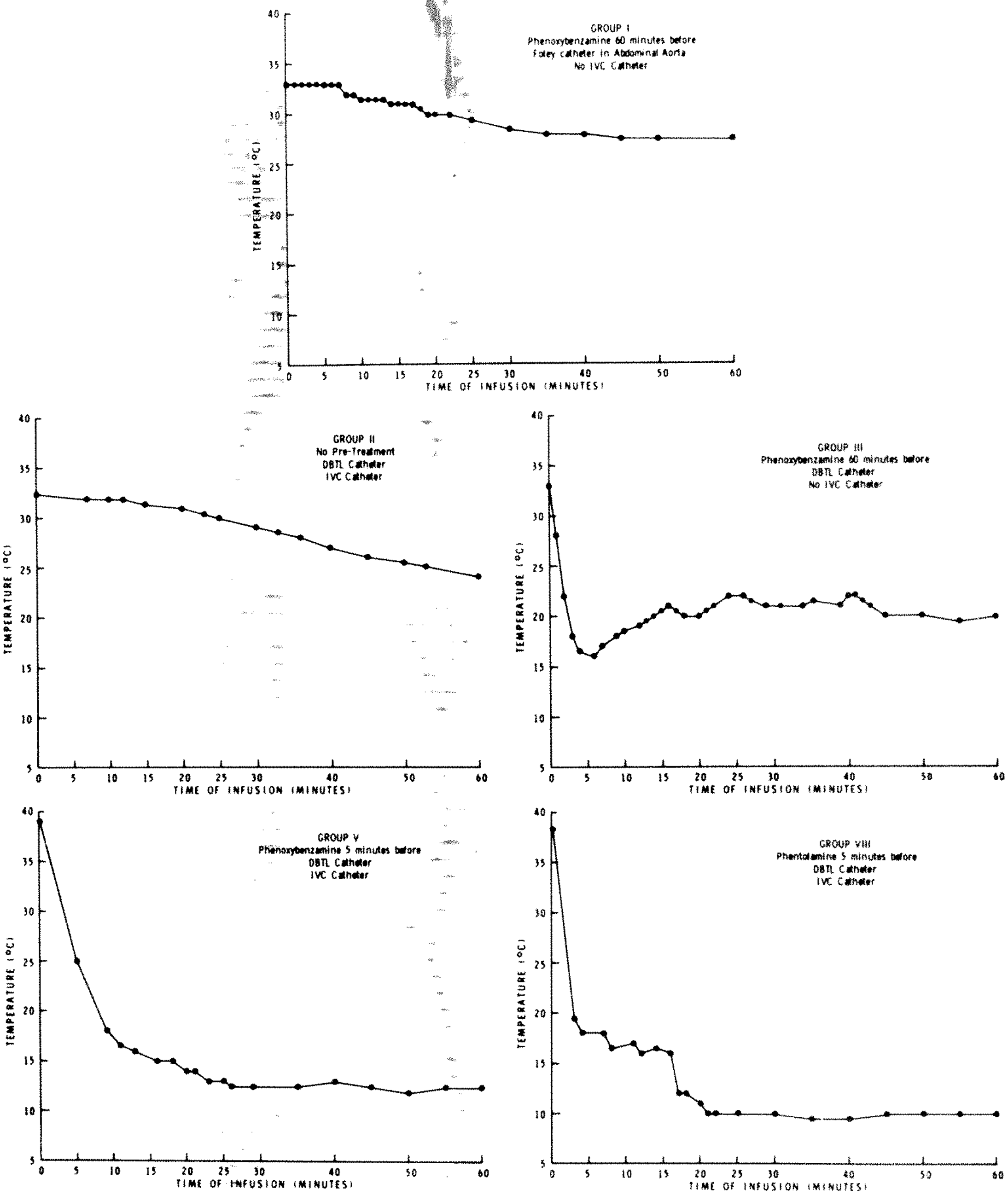

FIG. 4. Decrease in renal temperature after infusion of one animal of the various experimental groups. The results from groups IV, V and VI are similar (see Tables 1 and 3). Therefore, only one graph ("group V") is represented. Likewise the results in groups VII, VIII and IX are similar and only one graph is illustrated.

aorta and by noting disappearance of the pressure wave from the opposite femoral artery. We positioned the catheter correctly in every case. All dogs were sacrificed by injecting a lethal dose of sodium pentobarbital. After the EKG became isoelectric, we started the infusion.

We recorded: 1) initial renal and rectal temperatures, 2) decrease in renal and rectal temperature, 3) time required to decrease the kidney temperature to 15 C, 4) amount of infusate required to decrease kidney temperature to 15 C, 5) the lowest temperature to which we could cool the kidneys, 6) the time and amount of infusate required to attain this temperature, 7) the amount of infusate required to maintain the kidneys at this coldest temperature. For each dog the initial renal and rectal temperatures served as the control temperatures.

Experiments were designed to define the optimum conditions to effectively and reproducibly cool donor kidneys *in situ*, and to simulate experimentally clinical situations which could potentially be encountered. All animals were given 6 gm of mannitol, 1 mg/kg sodium heparin and 100 mg of methyl prednisolone (Solu Medrol)® Upjohn Laboratories,* intravenously. This pretreatment regimen was chosen to simulate the mannitol and cortocosteroids regimen frequently employed on pa-

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*Upjohn Laboratories, Kalamazoo, Michigan 49001

TABLE 2.

Group #	Description	Average rate of Temperature decrease to attain 15 C	Average amount of infusate required to attain 15 C	Average lowest temperature attained	Average amount of infusate required to maintain lowest temperature
I	Phenoxybenzamine pretreatment Foley Catheter in Aorta	—	—	27.8 C	No significant decrease
II	No pretreatment DBTL Catheter IVC Catheter	—	—	22.6 C	45 ml/min
III	Phenoxybenzamine pretreatment DBTL Catheter No IVC Catheter	—	—	21 C	43 ml/min
IV	Phenoxybenzamine 60 min before DBTL Catheter IVC Catheter	0.6°/min	4500 ml	14.5 C	148 ml/min
V	Phenoxybenzamine 5 min before DBTL Catheter IVC Catheter	0.8°/min*	1500 ml*	18.1 C	139 ml/min
VI	Phenoxybenzamine through catheter DBTL Catheter IVC Catheter	1.5°/min	1900 ml	14.3 C	130 ml/min
VII	Phentolamine 60 min before DBTL Catheter IVC Catheter	2.05°/min	1350 ml	9.8 C	140 ml/min
VIII	Phentolamine 5 min before DBTL Catheter IVC Catheter	0.93°/min	1750 ml	11.1 C	162 ml/min
IX	Phentolamine through catheter DBTL Catheter IVC Catheter	1.24°/min	1800 ml	12.3 C	170 ml/min

*One Dog.

tients with neurological trauma in order to decrease their cerebral edema.[5]

Only a brief explanatory note will be presented for each group of experimental animals (Table 1).

Group I (Control Group): Three dogs had a size 18 Fr Foley catheter inserted into the abdominal aorta to deliver the cold infusate. The Foley balloon was placed at the aortic bifurcation by the pull-back technique.

Group II: Three dogs had a DBTL Catheter inserted to deliver the cold infusate. A suction catheter was inserted into the inferior vena cava (IVC) to withdraw blood and infusate.

Group III: Three dogs underwent pretreatment with 1 mg/kg phenoxybenzamine, (Dibenzylene,® Smith Kline and French Laboratories)† in 250 ml of normal saline one hour before they were sacrificed. These dogs were infused with the DBTL Catheter but had no fluid withdrawal catheter inserted into the IVC.

All the dogs in experimental groups IV through IX had a DBTL catheter and an IVC suction catheter inserted. We attempted to determine the effect of two different alpha adrenergic blockers on renal cooling and how the mode of administering these two blockers would influence the rate of temperature decrease and eventual kidney function.

Group IV: Three dogs were pretreated with phenoxybenzamine one hour prior to infusion.

Group V: Three dogs were given phenoxybenzamine by intravenous administration five minutes before infusion.

Group VI: Three dogs were sacrificed 5 minutes after DBTL and IVC catheters were inserted. Then a bolus dose of phenoxybenzamine (1 mg/kg) and the cold infusate was introduced through the DBTL Catheter.

Experimental groups VII through IX were designed to test whether phentolamine, (Regitine,® CIBA Pharmaceuticals)* rather than phenoxybenzamine, could be used as an effective blocking agent since phenoxybenzamine is available only for experimental purposes. We gave a 0.5 mg/kg dose of phentolamine intravenously. In groups IV and VII, V and VIII, and VI and IX we used the same experimental design except for replacing phenoxybenzamine with phentolamine.

Results

A. *In situ renal cooling by infusion via Foley Catheter* (Group I) (Fig. 4, Table 2).

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†Smith, Kline and French Laboratories, 1500 Spring Garden St., Philadelphia, Pa. 19101

*CIBA Pharmaceutical Company, Summit, New Jersey, 07901.

The average rate of temperature decrease for this group was .08 C per minute for both renal and rectal temperatures. After one hour of infusion, the lowest renal temperature attained by any animal was 27.8 C.

B. *In situ renal cooling with the DBTL Catheter, IVC Catheter inserted, no adrenergic blocker pretreatment* (Group II) (Fig. 4, Table 2).

Renal temperatures decreased at an average rate of 0.13 C perminute. The lowest renal temperature attained in any of the experimental animals was 20 C after 1.5 hours and administration of 4500 ml of infusate. Rectal temperature was not significantly decreased with use of the DBTL Catheter.

C. *In situ renal cooling after adrenergic blockage with phenoxybenzamine.*

1. *Phenoxybenzamine pretreatment one hour prior to infusion, no IVC Catheter* (Group III) (Fig. 4, Table 2). There was a rapid decrease in renal temperature. The lowest temperature averaged 21 C after 14.8 minutes of infusion administration. Although the overall average rate of renal temperature decrease was 1.38 C/min, the lowest temperature achieved was 16 C and this occurred in only one dog during a one hour infusion. We could not further reduce renal temperature possibly because we could not administer large volumes of infusate.

The maximum average infusion rate was 43 ml/min. because we were infusing into a closed system. To attempt to increase the infusion rate, we then introduced a catheter into the inferior vena cava to provide an egress for the blood and infusate and to determine whether large volumes of infusate could be administered.

2. *Phenoxybenzamine treatment or pretreatment with infusion through a DBTL Catheter and IVC Catheter inserted* (Groups IV, V, VI).

We achieved effective, rapid renal cooling in these three groups (Fig. 4, Table 2). Though the rate of renal temperature decrease to 15 C was almost twice as fast in animals receiving phenoxybenzamine through the catheter (group VI), the lowest average renal temperature attained in the three groups was similar: 14.5 C, 18.1 C, and 14.3 C respectively. The amount of infusate required to maintain this temperature was also similar, 148 ml/min, 139 ml/min and 130 ml/min.

D. *In situ renal cooling after alpha adrenergic blockade with phentolamine, DBTL Catheter, IVC Catheter inserted* (Groups VII, VIII, IX).

We achieved effective, rapid renal cooling using this mode of treatment as well (Fig. 4, Table 2). The lowest average temperatures we attained were 9.8 C, 11.1 C and 12.3 C, slightly lower than in the phenoxybenzamine treated group. The rates of renal temperature decrease to 15 C were 2.05 C/min, 0.93 C/min and 1.24 C/min. The rates of infusion required to maintain these temperatures were approximately the same: 140 ml/min, 162 ml/min and 170 ml/min.

Renal Perfusion Studies

We performed a bilateral nephrectomy on one dog from Group IV one hour after infusion with the DBTL Catheter. The kidneys were perfused at 10 C for 3 hours in a Belzer Perfusion® apparatus. Perfusion pressures averaged 40/20 mmHg and flows exceeded 125 ml/min/kidney. After perfusion, a renal arteriogram demonstrated normal renal vasculature.

One kidney was examined using both light and electron microscopy. These examinations revealed intact, normal renal architecture. The other kidney was transplanted into another dog and functioned until the tenth postoperative day. Urine flow ceased due to rejection as determined by histologic examination of the kidney.

Clinical Studies

Pilot Study: Ten cadaver donors underwent rapid nephrectomy after cessation of cardiac action. Death in all cases had been due to blunt or penetrating trauma. At the time of arrival at the emergency center the patients had clinical evidence of neurological death, unstable cardiovascular system and a satisfactory urine output. Cardiac standstill occurred before EEG's could be obtained.

At the time of cardiac arrest, 200 mg phenoxybenzamine was administered intravenously. All patients were given external cardiac massage and had respiratory support while being transferred to the operating room. The duration of warm ischemia from the moment of cardiac arrest until completion of nephrectomy ranged between 35 to 90 minutes.

After the donor's nephrectomy, all kidneys were perfused in a Belzer Perfusion® apparatus. Eighteen kidneys had high perfusion pressures and low flows, less than 50 ml/min/kidney and were unsuitable for transplantation. The two other kidneys perfused adequately and functioned after transplantation.

Clinical studies with the Double-Balloon-Triple-Lumen Catheter: We used catheter infusion on 11 different donors who manifested acute neurological death and had an unstable cardiovascular system. We did not use the IVC Catheter to withdraw blood and infusate from the first 3 donors. Using the IVC Catheter in the other 8 donors, we obtained higher infusion rates and temperatures as low as those achieved in dogs.

We administered 200 mg Phenoxybenzamine intravenously to 10 of the 11 donors at the first sign of agenal EKG change. In one case both DBTL and IVC Catheters were inserted into a donor who had been without cardiac action for approximately 8 minutes and had not received dibenzylene or phentolamine. Though the kidneys from this donor cooled to 15 C, they never functioned

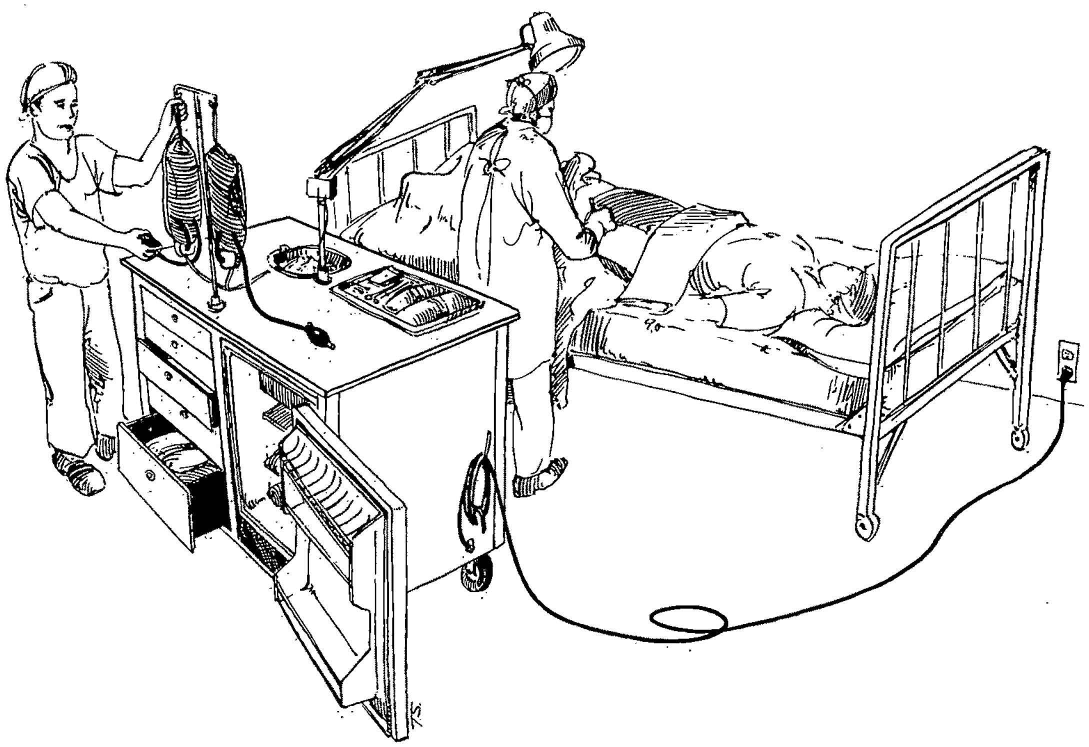

FIG. 5. The module used for insertion of the DBTL catheter is transported to the donor's bedside.

adequately in the perfusion machine. They had poor flow and high perfusion pressure, so they were not used for transplantation.

In another donor, the proximal balloon broke. The renal temperature was 27 C at the time of nephrectomy in spite of administration of 5000 ml of cold infusate. Since neither kidney functioned adequately in the perfusion apparatus, they were both discarded.

The temperature of the kidneys from the remaining 9 donors ranged from 15 C to 22 C at the time of nephrectomy. The time elapsed from cardiac standstill to completion of the second nephrectomy was between 45 to 90 minutes with the average time elapsed, 59 minutes. Between 2500-10,000 ml infusate was administered during this time with an average of 6000 ml.

Perfusion of all kidneys was satisfactory. All were transplanted and all produced urine immediately after surgery.

Catheter insertion was facilitated by a specially designed module* (Garcia-Feldman Cadaver Organ Preservation Cart) which can be wheeled to the donor's bedside (Figs. 5 to 7). When the patients were transferred to the operating room for nephrectomy, the ice bucket containing the cooling coil and the infusion apparatus were transferred to the donor's bed while the module remained at the emergency center.

Discussion

We have developed a catheter for the rapid *in situ* preservation of cadaver kidneys. This catheter has several important characteristics: 1) It can be inserted without fluoroscopic assistance; 2) Ectopic and/or multiple renal arteries can be simultaneously infused; 3) The equipment required for satisfactory infusion is readily available in any hospital. Three catheters, designed for use in various age groups, are currently available.

The catheter prototype has multiple openings between the occlusion balloons to allow adequate infusion of multiple renal arteries which we found in 15% of the cadavers dissected. The multiple openings allow the concurrent cooling and probable functional preservation of other abdominal organs which may be suitable for transplantation in the future. During the course of our experiments, we noted that the liver, pancreas and small bowel were also cooled. Their temperatures were always 3 C to 4 C higher than kidney temperatures.

We tried to keep the infusion system simple. The Garcia-Feldman Cadaver Organ Preservation Cart was constructed for convenience and is not required with the DBTL Catheter. Effective, rapid renal cooling of kidneys in experimental animals can be accomplished by high flow infusion (> 130 ml/min) of a solution at 4 C, with an egress for the infusate after administration of an alpha adrenergic blocker.

The particular infusate composition is not essential for successful preservation of renal function after *in situ* cooling according to Sullivan.[9] Since we used the Ringer's lactate—Na HCO_3—lidocaine solution to flush kidneys removed from living related and "beating heart donors" at our institution, we arbitrarily chose to use the same solution as the infusate for this study.

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*Module specifications can be obtained from Mr. Louis Feldman, Department of Surgery, Baylor College of Medicine, Houston, Texas.

Administration of an alpha adrenergic blocker facilitated both renal cooling and the maintenance of decreased organ temperature. Alpha adrenergic blockers allowed higher infusion rates and consequently better heat exchange and effective renal cooling in all the experimental groups in which we used them. From our results it appears that the type of block or its mode of administration is not critical.

Our experimental data do not support any advantage to giving the alpha adrenergic block one hour before cessation of cardiac action. However, Belzer found a reduction in post-transplant acute renal insufficiency when phenoxybenzamine is given one hour previous to cessation of cardiac action.[2] We currently use phenoxybenzamine pretreatment, until we can prove clinically that administration of the block through the catheter will accomplish similar results.

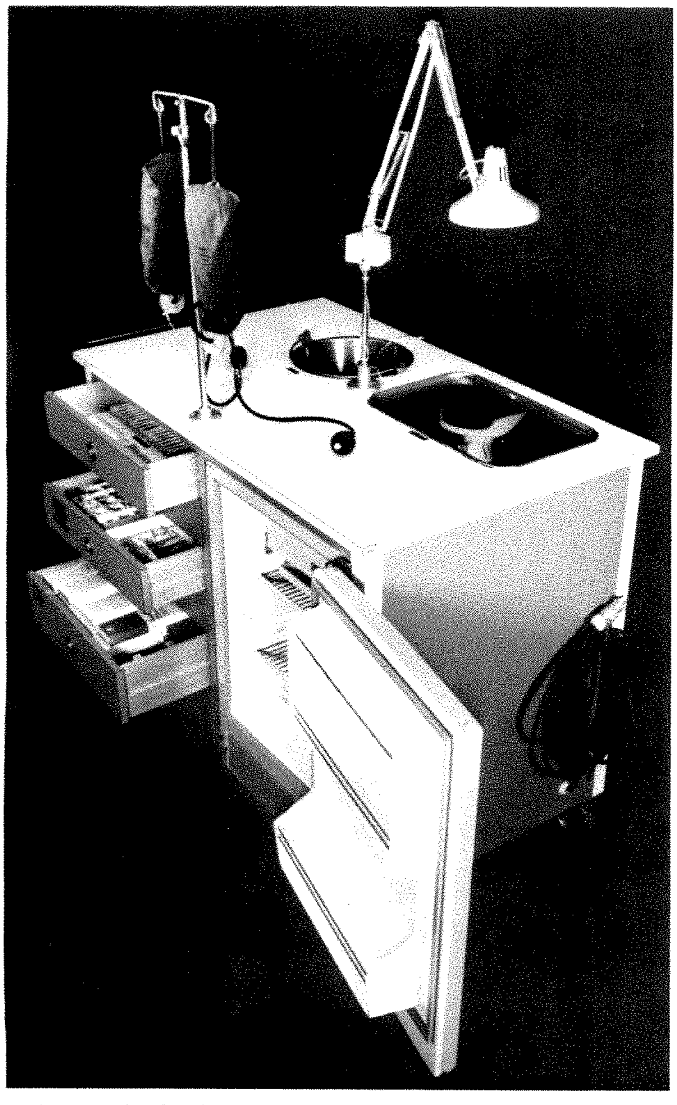

FIG. 6. The Garcia-Feldman Cadaver Organ Preservation Cart.

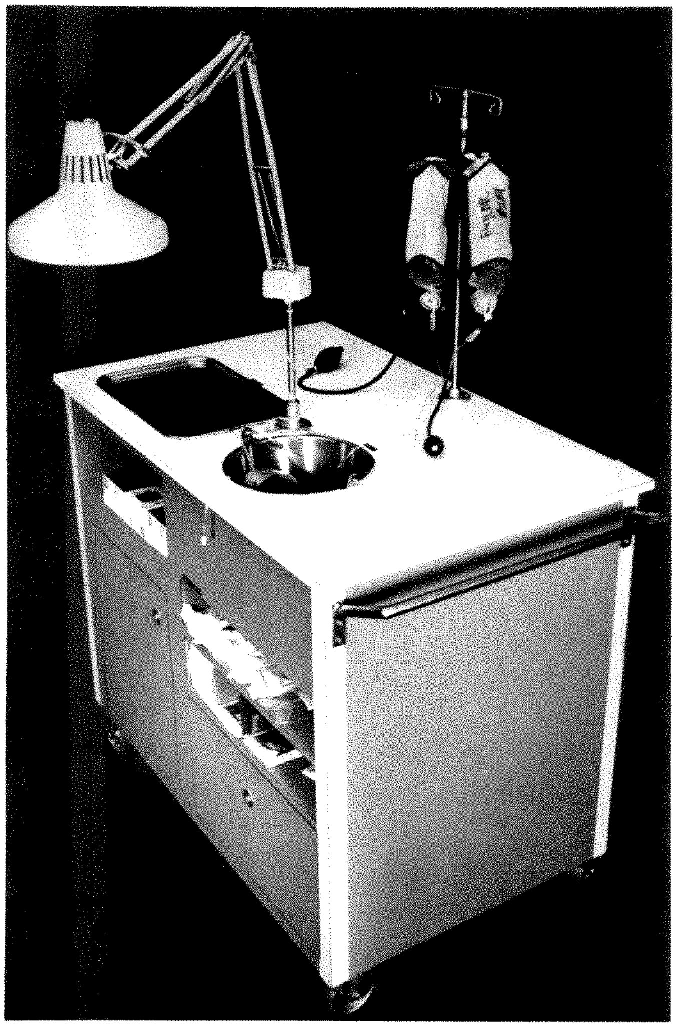

FIG. 7. The Garcia-Feldman Cadaver Organ Preservation Cart.

With our initial human donors a "one way" infusion system proved inadequate to cool the kidneys to 10-15 C to significantly reduce the renal metabolic demands. We traced the source of this problem to our inability to deliver the infusate at a high rate of infusion. A suction catheter inserted into the inferior vena cava provided an egress for the donor's blood which allowed higher infusion rates and more effective cooling.

We have used the Double-Balloon-Triple-Lumen Catheter successfully in our clinical transplantation program. It has provided additional unforeseen benefits. Some families are more willing to authorize organ donations if the physician can reassure them that nephrectomy will be performed only after cessation of cardiac action. It has also greatly facilitated the logistics of an immediate transplant nephrectomy in an already busy operating suite of a trauma hospital. Instead of rushing into the operating room while performing external cardiac massage, then attempting to perform a hurried nephrectomy, the donor is now transferred to the operating room while being infused. A careful nephrectomy can be performed.

We still favor the use of the "beating heart donor" because of the shorter period of warm ischemia and lower incidence of post-transplant acute renal insufficiency. In view of Clark's recent evidence that extracorporeal perfusion may be harmful to harvested kidneys,[4] perhaps organs obtained from "beating heart donors" should be preserved by cold storage. However, for kidneys obtained from donors who undergo cardiac arrest and require insertion of the DBTL Catheter, a period of perfusion might be helpful to determine the physiologic suitability of the organ.

The number of kidneys obtained and the short postoperative period prevent us from drawing any conclusions regarding the possible long-term effects of the catheters on chronic renal function.

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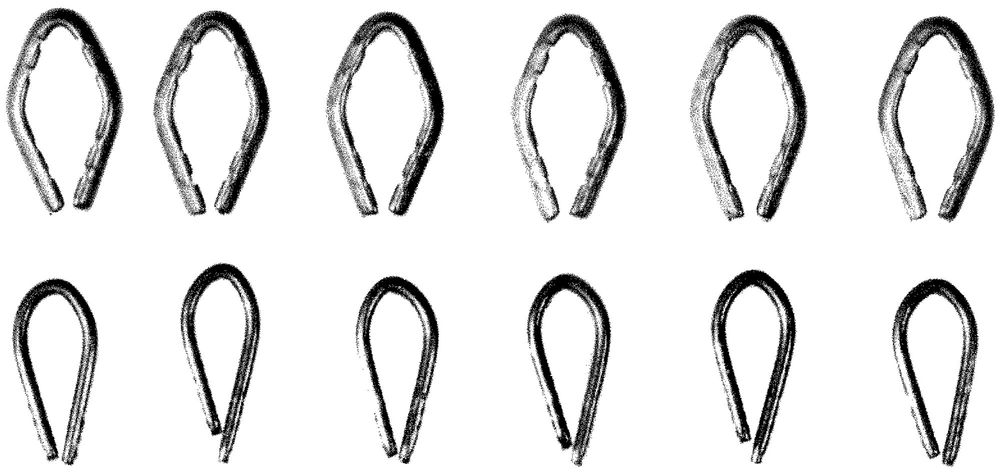

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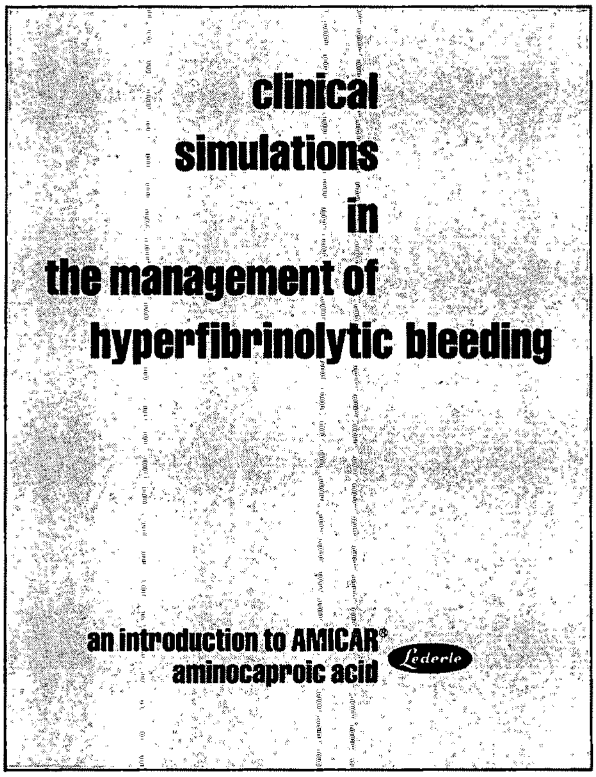
A new clinical simulation on the control of life-threatening hyperfibrinolytic hemorrhage



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ANS

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INTRAVENOUS • TABLETS • SYRUP

INDICATIONS: AMICAR has proved useful, in many instances, in the treatment of excessive bleeding which results from *systemic hyperfibrinolysis* and *urinary fibrinolysis*. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Systemic hyperfibrinolysis, a pathological condition, may frequently be associated with *surgical complications* following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; *hematological disorders* such as aplastic anemia, *abruptio placentae, hepatic cirrhosis, neoplastic disease* such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is *surgical hematuria* (following prostatectomy and nephrectomy) or *non-surgical hematuria* (accompanying polycystic or neoplastic diseases of the genitourinary system).

CONTRAINDICATIONS: AMICAR should not be used when there is evidence of an active intravascular clotting process.

WARNINGS: Safe use of AMICAR has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of child-bearing potential and particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible hazards.

PRECAUTIONS: AMICAR *aminocaproic acid* has a very specific action in that it inhibits both plasminogen activator substances and, to a lesser degree, plasmin activity. The drug should NOT be administered without a definite diagnosis, and/or laboratory findings indicative of hyperfibrinolysis (hyperplasminemia).[1]

[1] Stefanini, M. and Dameshek, W.: The Hemorrhagic Disorders. Ed. 2. New York, Grune and Stratton, pp. 510-514, 1962.

The use of AMICAR should be accompanied by tests designed to determine the amount of fibrinolysis present. There are presently available (a) general tests, such as those for the determination of the lysis of a clot of blood or plasma and (b) more specific tests for the study of various phases of fibrinolytic mechanisms. These latter tests include both semiquantitative and quantitative technics for the determination of profibrinolysin, fibrinolysin, and antifibrinolysin.

Animal experiments indicate particular caution should be taken in administering AMICAR to patients with cardiac, hepatic or renal diseases.

Demonstrable animal pathology in some cases have shown endocardial hemorrhages and myocardial fat degeneration. The use of this drug should thus be restricted to patients in whom the benefit hoped for would outweigh the hazard. Physicians are cautioned in the use of this product because of animal data showing rat teratogenicity and kidney concretions.

Rapid intravenous administration of the drug should be avoided since this may induce hypotension, bradycardia and/or arrhythmia.

One case of *cardiac* and *hepatic lesions* observed in man has been reported. The patient received 2 grams of aminocaproic acid every 6 hours for a total dose of 26 grams. Death was due to continued cerebral vascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

If it is accepted that fibrinolysis is a normal process, potentially active at all times to ensure the fluidity of blood, then it must also be accepted that inhibition of fibrinolysis by aminocaproic acid *may* result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of *intravascular clotting* which followed this treatment. Rather, it appears that such intravascular clotting was most likely a result of the fibrinolytic disease being treated.

It has been postulated that *extravascular clots* formed *in vivo* with incorporated aminocaproic acid may not undergo spontaneous lysis as do normal clots. However, it is the consensus of experts that the few reported cases of extravascular clotting could have occurred in the absence of aminocaproic acid treatment.

ADVERSE REACTIONS: Occasionally nausea, cramps, diarrhea, dizziness, tinnitus, malaise, conjunctival suffusion, nasal stuffiness, headache, and skin rash have been reported as results of the administration of aminocaproic acid. Only rarely has it been necessary to discontinue or reduce medication because of one or more of these effects.

Thrombophlebitis, a possibility with all intravenous therapy, should be guarded against by strict attention to the proper insertion of the needle and the fixing of its position.

DOSAGE AND ADMINISTRATION: *INITIAL THERAPY*—An initial priming dose of 5 grams of AMICAR administered either orally or intravenously followed by 1 to 1¼ gram doses at hourly intervals thereafter should achieve and sustain plasma levels of 0.130 mg./ml. of the drug. This is the concentration apparently necessary for the inhibition of systemic hyperfibrinolysis. Administration of more than 30 grams in any 24-hour period is not recommended.

INTRAVENOUS: AMICAR *aminocaproic acid* Intravenous is administered by infusion, utilizing the usual compatible intravenous vehicles (e.g. Sterile Water for Injection, physiologic saline, 5% dextrose or Ringer's Solution). RAPID INJECTION OF AMICAR INTRAVENOUS UNDILUTED INTO A VEIN IS NOT RECOMMENDED.

For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 16 to 20 cc. (4 to 5 grams) of AMICAR Intravenous be administered by infusion during the first hour of treatment, followed by a continuing infusion at the rate of 4 cc. (1.0 gram) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

ORAL THERAPY: If the patient is able to take medication by mouth, an identical dosage regimen may be followed by administering AMICAR Tablets or 25% Syrup as follows: For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 10 tablets (5 grams) or 4 teaspoonfuls of syrup (5 grams) of AMICAR be administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 gram) or 1 teaspoonful of syrup (1¼ grams) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

REV. 7/72

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2-1-5

CEA-ROCHE

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a valuable adjunct during the various phases of cancer management

CEA-ROCHE has been the subject of numerous clinical studies over the past four years to assess its value in cancer management. Most investigators have found this assay to be a useful biological marker for following the clinical course of patients with many types of internal carcinoma.* These studies have reported CEA-ROCHE to be a valuable adjunct in the overall evaluation of the patient's clinical progress and prognosis by indicating...

- lack of response to or escape from therapy
- need for a change or reevaluation of therapy
- development of metastases and/or local recurrence
- the need for more intensive patient examination and observation since a rise in CEA titer has been reported to precede other evidence of recurrence by periods averaging 2 months and up to as much as 29 months.*

CEA-ROCHE may also be used...

- as an adjunct to other diagnostic tests or procedures in the patient suspected of having cancer

*Literature available upon request from Professional Services Department, Roche Laboratories, 340 Kingsland Street, Nutley, N.J. 07110.

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CEA-ROCHE
Carcinoembryonic Antigen assay

Suggested Guidelines for the Use of CEA-ROCHE as an Aid in the Management of the Cancer Patient*

Type of Therapy	When to order CEA-ROCHE	Why order CEA-ROCHE
	During Periods of Active Therapy	
Surgery	As part of the presurgical workup and approximately 3 weeks after surgery	To monitor the effects of surgery[1-4]
Radiotherapy	Prior to initiating radiotherapy, once at midpoint and/or upon completion of radiation	To monitor the effects of radiation[1,2,5,6]
Chemotherapy	Prior to initiating chemotherapy, once at midpoint if therapy extends over a 6-week period and upon completion of chemotherapy	To monitor the effects of chemotherapy[1,2,5,7]
	During Short-term Follow-up After Therapy	
All types	Every 1 to 2 months during the first 6 months following therapy	To provide a basis for the reevaluation of therapy and/or an early indication of recurrence or progression of disease[1,2,8]
	During Long-term Follow-up	
All types	Every 6 to 12 months	To provide an early indication of recurrence or progression of disease[1,4,9,10]
	During Active Change in Clinical Condition	
All types	Every two weeks until trend is established	To aid in determining the probable presence of metastases or local recurrence[1,2,4,10]

When using this assay remember CEA-ROCHE is . . .

- *not* specific for any one type of cancer
- best used *periodically* to establish a trend, usually identifiable within 30 to 90 days
- *not* an absolute test for malignancy and should not be used as the sole criteria for diagnosis (use with other diagnostic tests and procedures)
- *not* recommended as a screen to detect cancer

*These are general guidelines for the use of CEA-ROCHE only and may vary widely depending on such factors as patient status, clinical symptoms, type of malignancy, results of other tests and procedures.

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ROCHE

ROCHE

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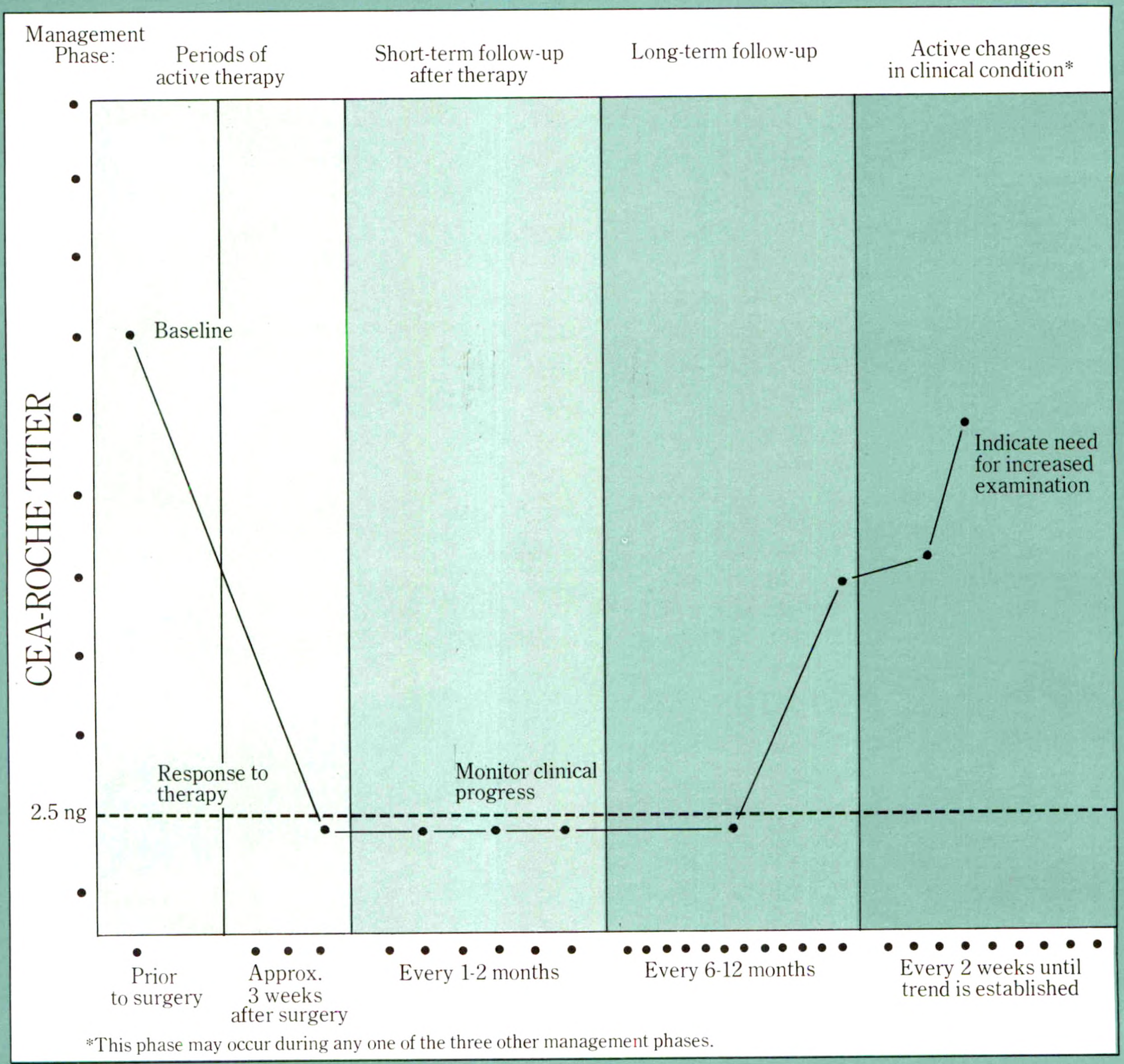

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Posterior Subcapsular Cataracts

Posttransplantation in Children

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Posterior subcapsular cataracts (PSC) were noted in 41 of 69 (60%) recipients of renal allografts. The PSC were noted during the first posttransplant year (Group 1) in 21 (30%) recipients and after the first posttransplant (Group 2) year in 20 (30%) recipients. The dosage of prednisone during the first posttransplant year corrected for patient weight showed a significant correlation with the development of PSC during the first posttransplant year. The severity of the PSC were correlated with time of onset and prednisone dosage. Four recipients in Group 1 required cataract extraction to obtain sufficient vision to facilitate school work.

IN THE PREVIOUS REPORTS devoted to renal transplantation in children,[3,7,11,16,21,24,26,29,33,38] only 2 describe the occurrence of posterior subcapsular cataracts (PSC) following transplantation. Belzer et al.[3] noted PSC in 16 of 53 (30%) recipients. The authors indicated that the the development of PSC were not related to the administration of corticosteroids and that no patient required cataract extraction because of visual impairment. In addition, Cerelli et al.[9] reported the presence of PSC in 2 of 31 (6.5%) recipients. No data were given relative to etiology or severity.

This report relates the incidence, severity and relationship of corticosteroid dosage to the development of PSC in 69 pediatric allograft recipients followed at Childrens Hospital of Los Angeles who had a functioning graft for at least 1 year.

Methods and Materials

Between February, 1967 and June, 1973, 86 recipients aged 1½ to 20 years received 108 renal allografts from 29 live related, 3 live unrelated and 76 cadaver donors. All of the live related and live unrelated grafts were first transplants. Immunosuppressive therapy consisted of azathioprine and prednisone as previously described (13). Rejection was treated initially by increasing the dosage of oral prednisone. Since 1971, rejection has been treated with intravenous methylprednisolone (30 mg/Kg daily for 3 days).

Of the 86 patients, 70 survived at least 1 year with a functioning allograft. Routine ophthalmoscopic examination was performed prior to transplantation and at each posttransplant clinic visit. Evidence of PSC was noted and recorded. Except for 1 patient whose original kidney disease was focal glomerulosclerosis for which she received corticosteroids for varying periods of time prior to transplantation, no patient had PSC prior to transplant.

Subjective visual impairment was determined at each clinic visit, and if present, complete ophthalmalogic examination was undertaken by one of us (W.A.W.).

Results

The 69 recipients were divided into 3 groups with regards to the development of PSC. Group 1 developed PSC during the first posttransplant year; Group 2 developed PSC after the first posttransplant year; and Group 3 had no PSC noted during the period of observation.

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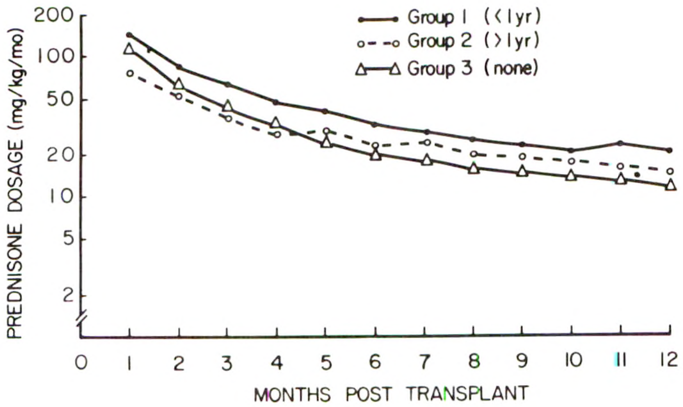

FIG 1. Posterior subcapsular cataracts in children.

A. *Incidence*

Of the 69 recipients, 41 (60%) developed PSC following transplantation. The PSC were noted during the first posttransplant year (Group 1) in 21 (30%) recipients, and after the first posttransplant year (Group 2) in 20 (30%) recipients. No PSC were detected during the 13 to 87 month observation period in the remaining 28 patients (Group 3).

B. *Time of Onset*

PSC were initially observed between the fifth and eleventh posttransplant month (7.3 ± 1.8 months) in the recipients in Group 1, and between the thirteenth and sixty fourth posttransplant months (36.0 ± 14.3 months) in the recipients in Group 2.

C. *Recipient Age*

The age of the recipients at the time of transplantation was similar in the 3 groups; Group 1 (11.5 ± 4.4 years), Group 2 (13.3 ± 3.9 years) and Group 3 (11.4 ± 4.0 years).

D. *Relationship to Prednisone Dosage*

The prednisone dosage received by the 3 groups of recipients during the first posttransplant year was correlated with development of PSC. There was no difference in the total yearly dose (Gms) (Fig. 1) of prednisone between the 3 groups of recipients (Table 1). However, when the weight of the patients was considered and the mg/Kg/mo (Fig. 2) dosage compared, there was a significant difference between the dosage received by the recipients in Group I and that received by the recipients in Group 2 ($p < .01$) and Group 3 ($p < .001$) (Table I).

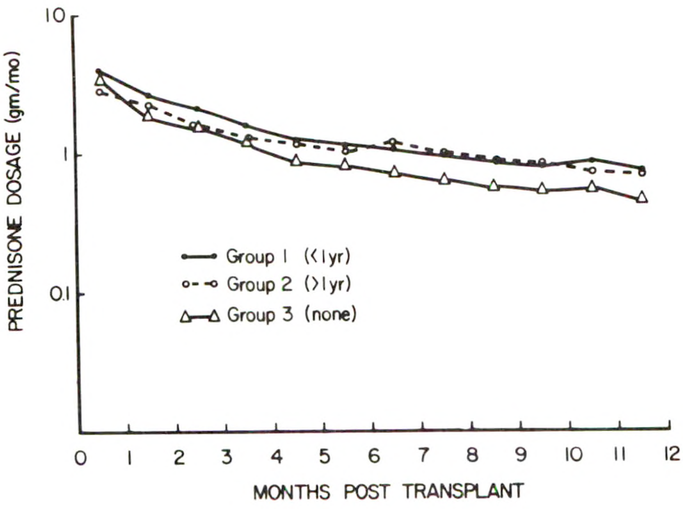

FIG. 2. Posterior subcapsular cataracts in children.

E. *Cataract Extraction*

The severity of the PSC correlated with the time of onset and therefore prednisone dosage. Four of the 21 (19%) recipients in Group 1 required cataract extraction because of visual impairment, whereas, no recipient in Group 2 needed surgery.

Case 1 (BD: 3/18/54) is a white male who received a second cadaveric graft on 10/29/72. PSC were first noted in May, 1973. Because of subjective visual impairment he underwent detailed ophthalmological examination in March, 1974. His vision was limited to hand motions without glasses. He was known to be myopic. His present glasses improved him to 20/200. His myopia had increased slightly and he was able to obtain 20/60 and 20/50 acuity with the two together, but only J-8 in either eye for near vision. His vision varied somewhat with lighting. With pupils dilated he could see at least 20/50 in each eye. Slit lamp examination revealed most of the posterior subcapsular area involved with a moderately dense cataract. The fundi were normal.

He was going to school and complained it was too difficult to continue unless his vision could be improved. On July 13, 1974, he had a discission of the right crystalline lens which matured the cataract and on July 20, 1974, underwent aspiration of the cataract and peripheral iridectomy. He was subsequently corrected to 20/20 vision and glasses were prescribed.

On December 21, 1974, phakoemulsification of the cataract of the left eye with peripheral iridectomy was performed. The left eye was improved to 20/20 vision and to J-2 with the correct reading addition.

Case 2 (BD: 2/15/53) is a white male who received a cadaveric graft on February 15, 1971. PSC were first noted in September, 1971. He underwent complete ophthalmologic examination on August 8, 1973. His vision was 20/80 uncorrected and 20/70 with a partial hyperopic correction. He had moderately dense posterior subcapsular cataracts by slit lamp examination. The fundi were normal. Post Cycloplegic refraction was 20/40 in each eye and 20/30 with the two together, but only J-8 in either eye. His visual acuity was worse in bright sunlight and vision was improved in the dark.

Re-examination six months later revealed no change in his visual acuity. The patient was having difficulty with his school work because of poor near vision. Dilating his pupils did not inprove his near vision.

On March 6, 1974, phakoemulsification of the left cataract was performed and subsequently he was improved to 20/20 vision and to J-2 with the reading addition. Corneal lenses were prescribed.

Case 3 (BD: 8/4/64) is a Mexican-American male who received a renal allograft from his father on October 10, 1972. PSC were first noted in March, 1973. Complete ophthalmological examination was initially performed on November 19, 1973.

Cycloplegic examination revealed plano in each eye with which he had 20/20 vision. There were diffuse but not particularly dense subcapsular cataracts of both eyes by slit lamp examination. The fundi were normal.

He was examined the following month and took a slight minus correction to obtain 20/40 vision. At this time he could read J-2 print without glasses at about 6 inches from his eyes.

Four months later his vision had slipped to 20/80 in each eye and minus lenses improved him to 20/50 and 20/60 and these lenses were prescribed.

Three months later although his vision was 20/40 and 20/50 he could read only J-5 right and J-8 left with or without dilated pupils. His cataracts were more dense, and therefore, phakoemulsification of the right cataract was performed on September 20, 1974. Subsequently he has been refracted to 20/20 vision in that eye and to J-2 with a ±2.50 add. The left eye has not been operated as yet.

Case 4 (BD: 6/9/59) is an American-Indian female who received a cardaveric graft on November 30, 1972. PSC were first noted in August, 1973. Detailed ophthalmologic examination was initially performed on August 26, 1974. Her vision was 20/200 uncorrected at this time. With the pupils dilated she revealed a minimal refractive error and could be improved to 20/50 right and 20/100 left. She could read J-2 with the right eye but complained of difficulty with school work because of variation in lighting. Pupillary dilation produced no improvement.

TABLE 1. *Relationship of Prednisone Dosage During 1st Posttransplant Year and Occurrence of PSC*

	Prednisone Dosage	
GROUP	mg/kg/mo MEAN ± S.D.	YEARLY DOSE (gm) MEAN ± S.D.
1 (<1 yr)	54.9 ± 30.6	21.7 ± 8.5
2 (>1 yr)	39.2 ± 17.0	19.4 ± 7.8
3 (None)	40.8 ± 18.7	17.2 ± 8.4
1 vs. 2	P<0.01	P=0.20
1 vs. 3	P<0.001	P=0.06
2 vs. 3	P=0.47	P=0.47

On February 28, 1975, phakoemulsification of the left cataract was performed which improved vision to 20/20 and J-2 with correction.

Discussion

Black et al.[6] in 1960, reported the development of PSC in patients with rheumatoid arthritis receiving corticosteroid therapy. This hitherto unrecognized association was correlated with both dosage and duration of corticosteroid therapy. In a follow-up study the same authors[30] reported a 42% (30 of 72) incidence of PSC in patients with various "rheumatic diseases" treated with long term corticosteroids. Patients receiving 15 mg or more of prednisone daily for more than a year had the highest incidence of PSC, whereas, treatment with < 10 mg of prednisone daily for < 1 year was unlikely to produce PSC. Subsequent reports were conflicting, with some authors failing to demonstrate the association[1,2,17,18,22,25,31,36] and others confirming the relationship.[10,14,15,35,39] In addition, the mechanism by which corticosteroids cause PSC was not apparent and an attempt to produce the lesion in the rat lens with systemic corticosteroid administration for a period of 16 weeks was unsuccessful.[37]

PSC were observed in children in the initial reports linking PSC to corticosteroids; however, the first reports involving exclusively pediatric patients appeared in 1965. Dikshit and Avasthe[12] observed PSC in 2 of 8 children

TABLE 2. *PSC in Children*

Author	Patients	Age (yrs)	Number PSC	%PSC	Onset PSC (mos)	Number Extractions	PSC Correlated with Corticosteroid Dosage
Dikshit & Avasthe (1965)	8	1½-11	2	25	2- 12	0	No
Havre (1965)	14	6-17	3	21	36- 72	0	No
Braver et al. (1966)	27		8	30		0	Yes Duration
Bihari & Grossman (1968)	67	8-19	13	19	13-104	0	Yes Dosage & Duration
Mino, et al. (1969)	45	4-20	22	49	<6->24	0	Yes Dosage
Lin, et al. (1971)	13	5-15	5	39	4- 6	0	Yes Duration
Kobayashi, et al. (1974)	35	3-14	10	29	7- 65	0	Yes Dosage & Duration

TABLE 3. *PSC Posttransplant*

Author	Patients	Age (yrs)	PSC	%PSC	Onset PSC (mos)	Extractions	PSC Correlated with Corticosteroid Dosage
Hovland & Ellis (1967)	26	11-50	12	46	8-28	1	No
Kern, et al. (1970)	28	10-50	9	32	3-43	0	No
Porter, et al. (1970)	39	17-50	9	23		0	Yes
Berkowitz, et al. (1973)	44			34			
	23	< 25	11	48		0	No
	21	26-49	4	19		0	No

with the nephrotic syndrome, and Harve[19] detected PSC in 3 of 14 children receiving long term (3 to 6 years) corticosteroid therapy. Of the 2 children with PSC in the former report,[12] 1 received 5 mg of prednisone daily for 1 year and the other 15 mg of prednisone daily for only 2 60 day periods. Neither report was able to correlate the development of PSC with either the duration or dosage of corticosteroids.

Subsequent reports[5,8,23,27,28] revealed an incidence of PSC in children receiving corticosteroids of 19 to 49% (Table II). The appearance of PSC after initiation of therapy varied from <6 months to >8 years. Visual impairment was minimal in the affected children and no child required cataract extraction. In 2 reports[27,28] the authors observed regression or disappearance of the PSC following discontinuation of corticosteroid therapy. Correlation between the development of PSC and either duration or dosage of corticosteroid administration or both, was apparent in all the latter reports (Table II).

The development of PSC in renal allograft recipients was initially investigated by Hovland and Ellis[20] (Table III). The authors observed a 46% incidence of PSC in 26 recipients. PSC were initially detected between the eighth and twenty eighth posttransplant month. No correlation was found between the development of PSC and corticosteroid dosage. In addition, the authors attempted to produce PSC in the rat lens with parenteral prednisone and/or azathioprine for 3 months without success. Three additional reports[4,32,40] confirmed the occurrence of PSC in renal allograft recipients with an incidence of 23 to 34% (Table III). Only 1 report was able to correlate PSC with the dosage of corticosteroids administered. Porter et al.[32] calculated the total steroid dosage for the first posttransplant year and found a significant correlation ($p=0.05$) between the corticosteroid dosage and the development of PSC. Unfortunately, the authors were unable to state the time when the PSC first appeared. Berkowitz et al.[4] noted a relationship between the dosage of prednisone and the severity of PSC in younger recipients (<25 years). The latter group of patients also had a higher incidence (48%) of PSC (Table III).

The incidence (60%) of PSC in the present series of pediatric allograft recipients is the highest reported and confirms the data of Berkowitz et al.,[4] regarding the increased incidence in younger recipients. The high incidence of PSC in the present series was possibly related to the dosage of prednisone administered when corrected for the body weight of the patient. A statistically significant correlation existed between the mean monthly dose of prednisone administered during the first posttransplant year corrected for weight (mg/Kg/mo) and the development of PSC during the first posttransplant year. Such a correlation was not apparent if the total yearly dose of prednisone was compared. The failure of previous investigators to correlate the development of PSC with corticosteroid dosage especially in younger recipients may have resulted from their failure to correct the dose for the weight of the patient.

Our studies also confirm the findings of Berkowitz et al.[4] that the severity of the PSC is related to the dosage of corticosteroids. Of the 21 recipients who developed PSC during the first posttransplant year, 4 (19%) had sufficient visual impairment to require cataract extraction. This group of patients received the highest dosage of prednisone corrected for body weight during the first posttransplant year. Except for 1 patient reported by Hovland and Ellis[20] who had PSC prior to transplantation, the above patients are the only allograft recipients requiring PSC extraction.

The high incidence of PSC and the severity, especially in those recipients manifesting PSC during the first posttransplant year, indicate the need for assiduous ophthalmologic surveillance of the pediatric allograft recipient.

The 4 recipients in the present series were severely handicapped because of PSC. School work was impaired because of poor close vision. Neither glasses nor pupil dilation produced adequate vision for ordinary reading. Mydriatric drops can improve vision in patients with central PSC; however, in our patients the cataracts were diffusely covering the posterior capsule and such therapy was ineffectual. Therefore, extraction was necessary in order to facilitate sufficient vision for school work.

Since it is unlikely that prednisone can be discontinued in the allograft recipient who develops PSC, alternate approaches are necessary which will either slow the progression or facilitate regression of the PSC. A recent report (34) indicated that alternate day prednisone may be associated with symptomatic improvement of PSC in allograft recipients without effecting deterioration of graft function. The mechanism by which corticosteroids produce PSC is unknown and therefore, no definitive approach to prevention is possible. If the development of PSC is directly related to corticosteroid dosage then reduction in daily dosage or institution of alternate day therapy should be effective in decreasing the incidence and severity; however, if PSC is related to individual susceptability, definitive therapy will have to await elucidation of the mechanism by which corticosteroids produce PSC.

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Operative Management of Pancreatic Pseudocysts in Infants and Children:

A Review of 75 Cases

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This report combines the findings and treatment in 15 infants and children with pancreatic pseudocysts with 60 additional cases from a literature review. The mean age at diagnosis was 7.5 years with pseudocyst being more common in boys (44:31). Sixty per cent were due to trauma, while in 32% the cause was unknown. Abdominal pain (68%), a mass (64%), and vomiting (52%) were the most frequent findings. The serum amylase was elevated and the upper gastrointestinal contrast study consistent with a mass in 88% of cases. Operative treatment included external drainage in 25 children (33%), cystgastrostomy or cyst-jejunostomy in 34 (45%), excision in 10 (13%) and miscellaneous procedures in 6 (8%). Complications were relatively few and there were no deaths recorded. Recurrence rate for cyst-gastrostomy was 4.7%, cyst-jejunostomy 7.6%, external drainage 8% and cyst-duodenostomy 50%. External drainage operations had prolonged cutaneous drainage. These observations suggest the appropriate operation is determined by the location and duration of pseudocyst. Internal drainage is preferred and avoids complications seen following resection and external drainage. Cyst-gastrostomy is effective when the pseudocyst is retrogastric and adherent to the stomach wall. Cyst-jejunostomy is most useful in instances in which the pseudocyst is not adherent to the stomach wall. Low recurrence rates and a zero mortality rate makes operative treatment highly acceptable therapy. Low recurrence rates are expected in childhood cases, (particularly related to trauma) due to an absence of underlying pancreatic disease and ductal obstruction.

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NUMEROUS ARTICLES have described the operative treatment of pancreatic pseudocysts in adults, however, a relatively limited experience with this condition has been reported in children. This report combines the methods of diagnosis and treatment in 15 infants and children with pancreatic pseudocysts managed at the James Whitcomb Riley Hospital for Children (Indiana University Medical Center) with 60 additional childhood cases from a literature review. The purpose of this report is to formulate an appropriate plan for early diagnosis and operative treatment of pancreatic pseudocyst in the pediatric age group.

Clinical Material

During a 22-year period (1951-1973) 15 children with pancreatic pseudocysts were treated at the Riley Children's Hospital.

Seventy-five reported instances of pancreatic pseudocysts in children (including these 15 cases) have been tabulated according to operation and listed in Tables 2A-2E. The mean age of the patients was 7.5 years with a range of 5 months to 17 years (Fig. 1). Pseudocysts occurred in 44 boys and 31 girls. The pseudocyst in 44 children (58.6%) was the result of blunt abdominal trauma. Automobile accidents as a passenger or pedestrian was the most common mechanism of injury while bicycle handlebar injuries accounted for 9 of these traumatic pseudocysts. The etiology was unknown in 24 cases, due to mumps in 3, hereditary pancreatitis in 2, while a gastric duplication and biliary tract disease were considered causative factors in one case each (Table 1). The time interval between injury and diagnosis was 139 days in the Riley Children's Hospital group with a range of 15 to 712 days.

A frequent symptom was abdominal pain (Fig. 2).

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TABLE 1. *Etiology of 75 Cases of Pancreatic Pseudocyst.**

	No. of Cases	Percent of Total
Trauma	44	58.7%
Unknown	24	32 %
Mumps	3	4 %
Hereditary Pancreatitis	2	2.7%
Gastric Duplication	1	1.3%
Biliary Tract Disease	1	1.3%

*Almost 60% are due to trauma, and in one-third the cause was unknown.

Generalized or epigastric abdominal pain was seen in 51 children (68%) and vomiting in 39 (52%). An abdominal mass was palpable in 39 of 61 patients (64%). Information concerning this physical finding was unavailable in an additional 14 cases. Fever was noted in 18 patients (24%) and ranged from 99 to 105 F.

The most useful diagnostic studies were the serum amylase determination and the upper gastrointestinal contrast series. Fifty-two of the 75 patients had serum amylase determinations. Forty-six of these 52 patients (88.4%) had significant hyperamylasemia while 6 children (11.5%) did not. One of the 6 children with a normal serum amylase level had an elevated urinary amylase level. Plain x-rays of the abdomen were usually of little help in making a specific diagnosis. Non-specific findings including adynamic ileus, presence of peritoneal fluid, and a "sentinal loop" were occasionally observed. Fifty of the 75 patients had upper gastrointestinal contrast studies performed. In 44 of 50 cases (88%), there was extrinsic compression or displacement of either the stomach, duodenum or colon consistent with a diagnosis of pseudocyst. Three children had a pleural effusion on x-ray examination of the chest. Two of these children had mediastinal extension of their pseudocysts.

Despite suggestive physical, laboratory, and x-ray findings, the diagnosis of pancreatic pseudocyst was frequently not considered prior to operation. The preoperative diagnosis was recorded in 48 cases. A correct diagnosis of pancreatic pseudocyst was made in 19 children (39.5%), a non-specific diagnosis of "abdominal cyst" in 6 (12.5%), and a variety of incorrect diagnoses in 23 (48.0%). The preoperative diagnosis was not recorded in 27 cases. Of particular interest are 4 children who underwent operation for "acute appendicitis" and had the diagnosis of pancreatitis or pseudocyst missed at operation.

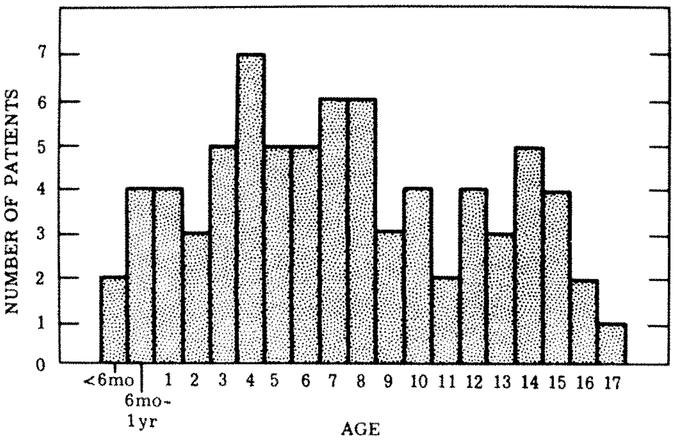

FIG. 1. Age distribution of 75 infants and children with pancreatic pseudocysts (mean age = 7.5 years).

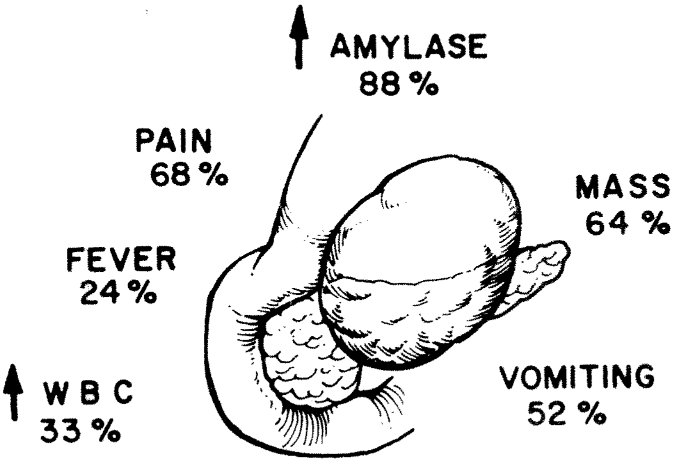

FIG. 2. Significant symptoms, clinical and laboratory findings in 75 cases of pancreatic pseudocysts.

Operative treatment included external drainage in 25 patients (33%), cystgastrostomy or cyst-jejunostomy in 34 patients (45%), excision in 10 patients (13%), and miscellaneous procedures in 6 (8%) (Fig. 3). All of the 75 patients in this review survived. Two of 25 children with external drainage procedures had recurrences (8%). One

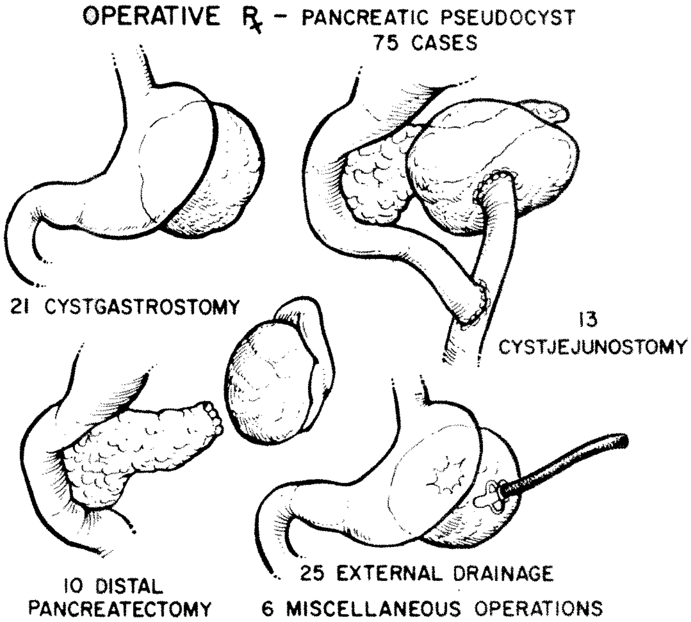

FIG. 3. Procedures performed in 75 instances of pancreatic pseudocyst in the pediatric age group.

TABLE 2A. *External Drainage*

Year, Author	Age, Sex	Preop. Diagnosis	Etiology	Length of Drainage
1909, Telling-Dobson[42]	11 mon, F	Abdominal cyst	Unknown	Unknown
1922, Drennen[14]	4 yr, M	Pancreatic cyst	Wagon wheel injury	17 days
1925, McWhorter[31]	6 yr, M	Not stated	Wagon wheel injury	5 wks
1951, Mithoefer[33]	20 mon, F	Pseudocyst	Unknown	7 wks
1957, Blumenstock et al.[5]	6 yr, M	Pseudocyst	Trauma	Unknown
1958, Warren et al.[46]	4-5 mon, F	Abdominal cyst	Unknown	3 wks-1st op. 12 wks-2nd op.
1959, Covington[10]	8 yr, M	Pseudocyst	Blunt abdominal trauma	6 wks
1959, Covington[10]	14 mon, M	Not stated	Child (sibling abuse)	Unknown
1960, Oeconomopoulos[35] et al.	8 yr, F	Pseudocyst	Handlebar injury	7 wks
1963, Hillis[24]	5 yr, F	Pseudocyst	Trauma	Unknown
1964, DiCenso et al.[13]	4 yr, M	Not stated	Blunt abdominal trauma	2½ mon
1965, Hendren et al.[23]	13 yr, M	Pseudocyst	Congenital hemolytic anemia	9 mon
1967, Wool et al.[51]	3½ mon, M	Pseudocyst	Blunt abdominal trauma	Unknown
1967, Wool et al.[51]	6 yr, F	Pancreatitis	Blunt abdominal trauma-fall	5 wks
1968, Othersen et al.[36]	9 yr, M	Not stated	Handlebar injury	Unknown
1968, Otherson et al.[36]	11 yr, F	Not stated	Handlebar injury	5 mon
1968, Othersen et al.[36]	5 yr, M	Sub capsular rupture of spleen	Blunt abdominal trauma	22 days
1968, Othersen et al.[36]	8 yr, M	Not stated	Blunt abdominal trauma	31 days
1968, Othersen et al.[36]	2 yr, M	Hepatoma	Blunt abdominal trauma	26 days
1969, Bongiovi et al.[6]	5 yr, M	Not stated	Child abuse	30 days
1970, Eisenbaum et al.[15]	10 yr, M	(1) Appendicitis (2) Postop hemorrhage	Unknown	10 days
1973, Cloutier[8]	16 mon, M	Not stated	Secondary to gastric duplication	Unknown
1975, Cooney, Grosfeld*	2 yr, M	Ruptured viscus	Trauma	Unknown
1975, Cooney, Grosfeld*	13 yr, F	Ruptured viscus	Trauma	Unknown

*Present series

was treated with a second external drainage procedure which again failed. A cyst-jejunostomy finally drained this cyst successfully. The second patient's recurrence resolved after repeat external drainage. In 15 patients, where information was available, pseudocysts drained for a mean time interval of 59 days with a range of 10 to 252 days. Two additional patients still had draining cysts when lost to followup at 2 weeks and 4 months postoperatively. Ten patients had their pseudocysts successfully excised. One of these children subsequently developed insulin dependent diabetes mellitus. No other complications were observed.

Cyst-gastrostomy was performed in 21 of 36 patients with internal drainage procedures. One of 21 cases recurred. One patient in the Riley Children's Hospital series had one brief episode of postoperatively upper gastrointestinal hemorrhage which spontaneously subsided. Cyst-jejunostomy was performed in 13 patients. All but one was accomplished using the Roux-en-Y technique. One child had a loop cyst-jejunostomy with a distal side-to-side jejunostomy. One recurrence (7.6%) was encountered. Complications occurred in 3 cases and included an intra-abdominal abscess, sepsis, and bowel obstruction.

Two patients were treated by cyst-duodenostomy. One cyst recurred and was secondarily drained by cyst-gastrostomy. The other pseudocyst drained by cyst-duodenostomy was the result of hereditary pancreatitis. Continued abdominal pain 18 months later necessitated reoperation and performance of pancreatojejunostomy in this child.

Three patients had distal pancreatectomy. In addition, two of these patients had end-to-end pancreatojejunostomy while one had a complimentary Puestow procedure. No recurrences or complications were observed. One pseudocyst was drained by a transgastric tube without complication.

Discussion

In 1909, Telling and Dobson described external drainage treatment of an intra-abdominal cyst in an 11-month-old girl thought consistent with a pancreatic pseudocyst.[42] Some authors have questioned the authenticity of this "pseudocyst" and credit Drennen (1922) with the first well documented case concerning the surgical treatment of pancreatic pseudocyst in the pediatric age group.[14] During the following 50 years, only 59 additional operative cases in children have appeared in the English literature.

TABLE 2B. *Cyst Gastrostomy*

Year, Author	Age, Sex	Preop. Diagnosis	Etiology
1964, Miller[32]	6 yr, F	Retrogastric mass	Handlebar injury
1964, DiCenso et al.[13]	12 yr, M	Not stated	Handlebar injury
1965, Hendren et al.[23]	15 yr, M	Not stated	Blunt abdominal trauma
1966, Gallagan et al.[20]	10 yr, F	Not stated	Unknown
1967, Stone et al.[41]	2 yr, F	(1) perforated appendix (2) not stated (3) pseudocyst	Unknown
1967, Stone et al.[41]	3 mon, F	(1) not stated (2) not stated	Unknown
1967, Wool et al.[51]	19 mon, F	Pseudocyst	Unknown
1967, Wool et al.[51]	5 yr, F	Pseudocyst	Blunt abdominal trauma (auto accident) Recurred and drained again via cystgastrostomy successfully
1967, Rubinoff et al.[38]	7 yr, F	Pseudocyst	Handlebar injury
1969, Attard[3]	7 yr, F	Not stated	Unknown
1972, Tucker et al.[44]	8 yr, M	Pseudocyst of pancreas	Blunt abdominal trauma
1973, Moosa[34]	7 yr, F	Duodenal ulcer	Unknown
1973, Moosa[34]	12 yr, F	Peritonitis	Blunt abdominal trauma
1973, Moosa[34]	15 yr, M	(1) rupt. viscus (2) pseudocyst	Blunt abdominal trauma Blunt abdominal trauma
1973, Moosa[34]	12 yr, M	Delayed rupture of spleen	Blunt abdominal trauma
1973, Moosa[34]	16 yr, M	Pseudocyst	Blunt abdominal trauma
1975, Cooney, Grosfeld*	4 yr, F	Pseudocyst	Blunt abdominal trauma
1975, Cooney, Grosfeld*	10 yr, M	Pseudocyst	Unknown
1975, Cooney, Grosfeld*	10 mon, M	Pseudocyst	Unknown
1975, Cooney, Grosfeld*	14 yr, M	Pseudocyst	Trauma
1975, Cooney, Grosfeld*	16 yr, M	Pseudocyst	Trauma

*Present series

The 75 cases in the present review probably represent only a portion of the actual number of cases treated operatively. Some instances have been over-looked because of inclusion in adult series as well as those treated and unreported. The accumulated experience, however, is sufficient so that one can begin to draw some conclusions as to the expected clinical presentation and anticipated results of operative treatment of these lesions in infants and children.

Etiology

A significant difference in the etiology of pseudocysts in adult and pediatric patient populations has been observed.[21] Over 80% of pseudocysts in adults are due to complications of alcoholic pancreatitis.[43] In contrast, 59% of the 75 reviewed pediatric cases had an antecedent history of blunt abdominal trauma. The etiology of underlying pancreatitis in more than 32% of the pediatric patients remains obscure. Feldstein's recent report of pan-

TABLE 2C. *Cyst-Jejunostomy*

Year, Author	Age, Sex	Preop. Diagnosis	Etiology
1958*, Warren et al.[46]	4-5 mon, F	Abdominal cyst	Unknown
1958, Shore[40]	13 yr, M	Not stated	Unknown
1959, Welch[50]	10 yr, M	Pseudocyst	Trauma
1963, Cleveland et al.[9]	6 yr, M	Not stated	Trauma
1964†, DiCenso et al.[13]	9½ yr, F	(1) Appendicitis (2) Not stated	Unknown
1965, Hendren et al.[23]	6 mon, F	Not stated	Unknown
1973, Moosa[34]	8 yr, F	Choledocal cyst Pancreatic cyst	Unknown
1974, Feldstein et al.[16]	4 yr, M	Pancreatic pseudocyst	Mumps, pancreatitis
1975, Cooney, Grosfeld§	3 yr, M	Gastric duplication	Mumps, pancreatitis
1975, Cooney, Grosfeld§	15 yr, F	Pseudocyst	Trauma
1975, Cooney, Grosfeld§	12 yr, M	Not stated	Handlebar injury
1975, Cooney, Grosfeld§	4½ yr, M	Not stated	Trauma
1975, Cooney, Grosfeld§	14 yr, M	Pseudocyst	Trauma
1975, Cooney, Grosfeld§	17 yr, M	Pseudocyst	Trauma

*Originally drained externally
†Cyst-jejunostomy with jejunojejunostomy
§Present series (Three cases previously reported Kilman et al.[26])

TABLE 2D. *Excision*

Year, Author	Age, Sex	Preop. Diagnosis	Etiology
1948, McPherson et al.[30]	6 mon, M	Extra-renal, extra-alimentary cyst	Unknown
1955, Lussky[29]	3½ yr, M	Abdominal cyst	Unknown
1956, Levitsky et al.[28]	9 yr, M	Pseudocyst	Trauma
1960, Oeconomopoulos et al.[35]	4 yr M	Pseudocyst	Mumps, pancreatitis
1964, DiCenso et al.[13]	15 mon, F	Not stated	Unknown
1967, Wool et al.[51]	4 yr, F	Not stated	Unknown
1968, Otherson et al.[36]	7 yr, F	Ruptured spleen	Handlebar injury
1969, Frazer[17]	7 yr, M	Pseudocyst	Handlebar Injury
1975, Cooney, Grosfeld*	14 yr, F	Bleeding gastric ulcer	Unknown
1975, Cooney, Grosfeld*	3 yr, M	Pseudocyst	Trauma

*Present series

creatic pseudocyst and concurrent parotitis with rising mumps titers suggests that determination of mumps titer may improve diagnostic efficiency in selected cases.[16]

Hyperlipidemia, hypercalcemia, bilary tract disease and heredity have also been cited as causative factors in childhood pancreatitis.[11,12] Steriod therapy and more recently, the drug L-Asparaginase (used in the treatment of leukemia) have been associated with pancreatitis in childhood.[49] The exclusion of these conditions and medications is important as a history of trauma may often be difficult to obtain particularly in instances of child abuse.[6]

Diagnosis

Pseudocysts are usually associated with a symptom complex of pain, fever, and vomiting. Sixty-eight per cent of the children had abdominal pain, 52% had vomiting and 24% had fever. The clinical onset in patients with pseudocyst may be insidious. A 14-year-old girl in the Riley Children's Hospital series, who had a history of massive hematemesis, appeared at first examination to have peptic ulcer, gastritis, or esophageal varices rather than a pseudocyst. Furthermore, one patient in the Riley Children's Hospital series and three additional patients in the review underwent prior appendectomies for mistaken diagnoses of acute appendicitis. These cases emphasize the diagnostic difficulties that may exist at the time of initial presentation.

The presence of an abdominal mass (present in 64% of cases) and upper abdominal tenderness were the most consistent findings on physical examination. Laboratory data often demonstrated an elevated serum amylase (88.4%), leukocytosis (33%), and occasionally hyperbilirubinemia. Persistant hyperamylasemia is consistent with a diagnosis of pseudocyst even in the absence of an abdominal mass.[43] Determination of urinary amylase and the separation of amylase into its salivary and pancreatic components by electrophoresis are also useful diagnostic adjuncts.[18]

X-ray examination of the chest and abdomen is often helpful in achieving a diagnosis. Pleural effusion may be the only initial finding.[20,27] While plain abdominal x-ray findings are usually non-specific, the upper gastrointestinal contrast study was consistent with a diagnosis of pseudocyst in 44 of 50 cases (88%). Recent experience with ultra-sound echograms and selective arteriograms suggest that these studies may also improve diagnostic accuracy.[19,37,45] Ultrasound discerns between a cystic (pseudocyst) or solid (tumor) mass, while arteriography usually demonstrates an avascular mass in instances of pseudocyst.[19,37]

Treatment

The selection of appropriate surgical management should be determined by the location and duration of the pseudocyst. Many early reports emphasized the use of external drainage or marsupialization which was employed in one-third of these 75 cases. The largest single experience with external drainage was reported by Otherson et al.[36] who treated 5 children successfully by mushroom catheter drainage. Drainage persisted for 3 to 4 weeks in 4 patients and 5 months in another. One patient in the Riley Children's Hospital series was lost to followup while still draining 4 months postoperatively. In 11 other cases, the mean duration of drainage was 63 days. This is a somewhat shorter duration of drainage than seen with external drainage procedures in adults (mean = 6 months). The main objections to external drainage procedure is a high recurrence rate (22% to 24%) and prolonged persistance of fistula.[4,46] In addition, Anderson noted excessive losses of fluid and electrolytes and severe skin breakdown in 23% of cases when external drainage was employed.[2] These data, however, were obtained from observations in adults often with underlying chronic pancreatitis and ductal abnormalities and may not apply to instances of pancreatic trauma in children with previously normal glands. External drainage should remain the treatment of choice in those rare cases in which the cyst wall is thin and immature or evidence of abscess is encountered at operation. In the Riley Children's Hospital series of patients, the mean interval of time between injury and diagnosis was 139 days. This suggests that in children, the cyst wall is usually mature enough for operative anastomosis.

TABLE 2E. *Miscellaneous Operations*

Year, Author	*Age, Sex*	*Preop. Diagnosis*	*Etiology*	*Operation*
1966, Laird et al.[27]	15 yr, M	Not stated	Blunt abdominal trauma	Excision of tail-caudal Roux-en-Y pancreatico-jejunostomy
1968, Hellebusch et al.[22]	5 yr, F	Intra-renal mass	Blunt abdominal trauma	Excision of tail-caudal Roux-en-Y pancreatico-jejunostomy
1970, Dean et al.[12]	14 yr, F	Not stated	Unknown	Excision of tail-longitudinal pancreato-jejunostomy
1973, Moosa[34]	11 yr, M	Appendicitis	Blunt abdominal trauma	Cyst-duodenostomy
1973, Crane et al.[11]	7 yr, M	Pseudocyst	Hereditary Pancreatitis	Transgastric tube drainage with cyst-gastrostomy
1974, Appel[1]	8 yr, F	Not stated	Hereditary Pancreatitis	Cyst-duodenostomy*

*Continuing abdominal pain necessitated a Puestow procedure 1½ years later

Although no deaths had been reported in 10 patients following resection procedures, one child developed insulin dependent diabetes mellitus after excision which included the tail and part of the body of the gland. As a general rule, excision should be reserved for lesions that are small and located in the tail of the gland necessitating only a limited pancreatic resection.

In most instances of pancreatic pseudocyst, internal drainage procedures are preferred and avoid the potential complications related to partial pancreatectomy and the undesirable pancreaticocutaneous fistula frequently seen with external drainage. Prior to 1964, Miller noted that only 3 of 18 cases of pseudocysts in children had been drained internally.[32] Recently, however, internal drainage has been more frequently employed. In the 75 cases reported herein, 36 children (48%) had internal drainage procedures. The type of internal anastomosis used is chosen according to the location of the pseudocyst. Transgastric cyst-gastrostomy has been an effective form of therapy. Cyst-gastrostomy was accomplished in 21 children in this series with one recurrence observed. Becher,[4] in a collective review concerning 1,020 patients with pseudocysts, found cyst-gastrostomy to be associated with the lowest incidence of operative mortality and recurrence when compared to external drainage, excision, and other forms of internal drainage. Cyst-gastrostomy has the advantage of being a simpler and more readily accomplished technical procedure. It is most useful when the cyst is retrogastric and adherent to the posterior wall of the stomach. The theoretical disadvantage of this anastomosis is that it allows free access of hydrochloric acid and food particles into the cyst cavity. The excellent results observed in children following this procedure seem to outweigh its disadvantages. Another complication observed following cyst-gastrostomy is postoperative gastrointestinal hemorrhage which was observed in one child in the Riley Children's Hospital series. Hutson et al.[25] noted a 50% hemorrhage rate following cyst-gastrostomy and considered this directly related to the effects of gastric acid entering the cyst cavity. They further suggested that the edges of the stomach wall not be sutured so that they are not hindered from acting as a flap valve and thereby reduce the entry of gastric juices into the cavity.[25] In contrast, Schumer et al.[39] and Warshaw[45] report much lower rates (3%) of hemorrhage following cyst-gastrostomy and stress the importance of careful suture approximation to avoid hemorrhage. When cyst-gastrostomy is employed, we recommend the use of a tube gastrostomy for gastric drainage and keeping the patient without oral intake for approximately ten days. This prevents acid and food particles from entering the cyst and places the pancreas at rest.[21] During this time interval, the child may be maintained on peripheral hyperalimentation.

Kilman et al.[26] suggested that cyst-jejunostomy is the treatment of choice for pseudocyst as it avoids the problem of gastric contents entering the cyst. The Roux-en-Y loop technique was employed in 12 patients in the combined series. One additional patient had a loop cyst-jejunostomy with a distal side-to-side jejunojejunostomy. The major disadvantage of cyst-jejunostomy is that of a more complicated surgical procedure. One recurrence (8%) was noted in the children treated in this manner. This procedure is most useful in instances where the pseudocyst is not adherent to the stomach wall. Warshaw[45] reported recurrence rates of 3% following cyst-gastrostomy, 5% following cyst-jejunostomy and 8% after cyst-duodenostomy. These statistics are substantiated in Becher's review of 1,202 patients (mostly adults), where the recurrence rates were cyst-gastrostomy 2.3%, cyst-jejunostomy 4.5%, and cyst-duodenostomy 5.2%.[4] Warren et al.[47] found no difference between the effectiveness of cyst-gastrostomy or cyst-jejunostomy in the treatment of experimentally produced pseudocysts.

Although operative therapy is a more reliable method of treatment, Moosa and others have documented occasional successes with nonoperative management.[34] One child in Moosa's report, however, required 3½ months of hospitalization before symptoms resolved and the cyst decreased in size.

The low recurrence rates without a single mortality observed in 75 children with pancreatic pseudocysts makes operative treatment a thoroughly acceptable mode of therapy. Low recurrence rates should continue to be observed in children, especially in instances related to trauma due to an absence of underlying pancreatic disease and ductal obstruction.

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Surgical Treatment of 297 Soft Tissue Sarcomas of the Lower Extremity

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The results of surgical treatment of 297 soft tissue sarcomas arising in the lower extremity were critically examined. *En bloc wide soft part resection* (158 cases) yielded five and ten year survival rates of 63% and 50%. *Amputation or major disarticulation* (139 cases) gave corresponding survival rates of 45% and 29%. The most frequent cause of treatment failure was distant metastases, commonly in the lungs. The tissue type of sarcoma, histologic grade of malignancy, and tumor size appear to be important determinants of survival irrespective of the type of surgical treatment. Local recurrence of sarcoma occurred in 18% of the cases, more commonly after soft part resections than amputations. The proximity of a sarcoma to major vessels, bone or joint tends to compromise the margins of a wide soft part resection, thus increasing the risk of local recurrence. In appropriate cases, the scope of soft part resection can be extended by en bloc excision of the femoral vessels, with the hope of improving local control of sarcoma. Amputation should be resorted to if an adequate margin of resection cannot otherwise be obtained. This decision must be weighed against the high frequency of distant metastases in this disease. Postoperative adjuvant chemotherapy and immunotherapy offer prospects of prevention of this tragic outcome.

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THE LOWER EXTREMITY is the most common site for soft tissue sarcomas. These neoplasms often attain considerable size before being detected, for they tend to be obscured by the bulk of connective tissue and musculofascial structures from which they arise. While some differences in biologic behavior[6,8,10,12,13] are attributable to the tissue type of sarcoma, all pose similar problems in clinical management. Firstly, local recurrences are common after inadequate excision. These tumors are generally poorly circumscribed and, even if invested by a pseudocapsule, enucleation inevitably leaves behind gross or microscopic tumor.[2,3] Secondly, distant metastases develop with alarming frequency, sometimes within months of successful local control of the disease.

A frequent dilemma faced by the surgeon is whether to advise amputation or resection of only the soft tissues involved. To obtain some guidelines, a retrospective review of 20 years' experience with these tumors at Memorial Sloan-Kettering Cancer Center was carried out.

Materials and Methods

From 1949 to 1968, a total of 297 patients with soft tissue sarcomas of the lower extremity had definitive surgical treatment at Memorial Sloan-Kettering Cancer Center. One hundred sixty-one of these patients presented for initial therapy, while 136 came with locally recurrent disease after excision elsewhere. The minimum followup period is 5 years. Excluded from this study are 151 other patients seen at this center during the same period: 111 were found to have distant metastases on initial presentation, 17 were consultations only, 6 received palliative surgical therapy, and 17 underwent radiation therapy or chemotherapy.

The histologic diagnosis of sarcoma was established or confirmed at our Center in all instances. One of the authors (S.H.) reviewed all the available histopathologic material. Where appropriate, the histologic grade of malignancy was determined, based on cellular pleomorphism, cellularity and number of mitoses. Clinicopathologic characteristics of the tumor such as location, size and involvement of neurovascular structures, bone and joint were abstracted from the operative records and pathology reports. The frequency of local recurrence and metastases and the survival rate were computed with the clinicopathologic data and the method of treatment.

The surgical management of these neoplasms at Memorial Sloan-Kettering Cancer Center has been *wide soft part resection*[3,6] whenever possible. The tumor bearing structures are removed in monobloc fashion with one

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TABLE 1. *Size of Tumor* and 5-Year Survival*

	Large Tumors		Small Tumors		Frequency of Large Tumors
	Number	5-Year Survivors	Number	5-Year Survivors	
1. Thigh	112	51	34	18	77%
2. Leg	21	10	20	14	51%
3. Foot	2	1	8	7	20%
Total	135	62(46%)†	62	39(63%)†	

*Tumor size documented in 197 cases only. Tumors larger than 5 cm in diameter were regarded as large.
†$X^2=4.25$; $P<0.05$

tissue plane being beyond the confines of known or suspected tumor. For tumors occurring on or within muscle compartments, whole muscle groups from origin to insertion are resected with their investing fascia. *Amputation* or major disarticulation has been carried out mostly for bulky lesions involving a major bone, joint, vessel or nerve. The preferred level of exarticulation has been at least one joint above the site of the tumor so as to obviate recurrent disease in tissues contiguous with the tumor bearing area.

Results

Sex and Age

There were 159 male and 138 female patients, with a sex ratio of 1.15. The age ranged from 2 to 80 years with a median of 48 years. The frequency of occurrence increased for each decade from the first to reach a peak in the sixth decade, beyond which the frequency gradually decreased.

Site of Tumor

The thigh was by far the most common location of the tumor (211 cases). Next in frequency was the leg (60 cases), while the fewest tumors occurred in the foot (16 cases). The 5-year survival rates for tumors of the thigh (51%) were significantly worse compared to those for the leg (65%) and the foot (75%).

Size of Tumor

The size of the tumor was accurately documented in 197 cases. The dimensions were known in those cases in which primary surgical treatment was carried out at Memorial Center; data were incomplete with regard to patients who had had one or more attempts at resection in other hospitals. The maximum diameter of these neoplasms ranged from 1.5 cm to 40 cm. Tumors measuring 5 cm or more were arbitrarily classified as large. Table 1 shows the distribution of large and small tumors and the relationship of size to survival rate. As one would expect from the distribution of soft tissues in the lower extremity, the thigh yielded the highest proportion of large tumors (77%) when compared with the leg (51%) and foot (20%). Large tumors, taken as a group, gave a less favorable prognosis compared to small tumors, the 5-year survival rates being 46% and 63% respectively. This difference in survival is statistically significant ($P<0.05$).

TABLE 2. *Location and 5-Year Survival Rate According to Histologic Type of Sarcoma.*

	Thigh	Leg	Foot	Total All Sites	5-Year Survival Rate
Liposarcoma	67	14	1	82	56%
Fibrosarcoma	37	23		60	70%
Rhabdomyosarcoma	39	12	1	52	48%
Synovial Sarcoma	28	5	9	42	45%
Malignant Schwannoma	14	2		16	63%
Leiomyosarcoma	7			7	(3/7)
Angiosarcoma	6			6	(2/6)
Undifferentiated Sarcoma	13	4	4	21	57%
Miscellaneous Sarcomas	10		1	11	45%
Total	221	60	16	297	55%

Histologic Type of Sarcoma

Table 2 lists the histologic types. Liposarcoma, fibrosarcoma, rhabdomyosarcoma, and synovial sarcoma were the commonest, contributing 28%, 20%, 18% and 14% respectively to the total. Next in frequency were the giant and spindle cell sarcoma and other undifferentiated sarcomas (7%). There were 16 malignant schwannomas, 7 leiomyosarcomas, 6 angiosarcomas, and 11 miscellaneous sarcomas. The latter group consisted of 3 malignant fibrous histiocytomas, 3 extraosseous osteogenic sarcomas, 1 alveolar soft part sarcoma, 1 clear cell sarcoma, 1 malignant mesenchymoma and 1 malignant giant cell tumor.

Prognosis varied with the histologic type of sarcoma. The 5-year survival rate of the whole series was 55%. However, patients with fibrosarcomas had a 5-year survival rate of 70%, while those who had rhabdomyosarcomas, synovial sarcomas as well as less commonly encountered types of sarcomas had survival rates of about 45% or lower.

Histologic Grade of Malignancy

The liposarcomas and fibrosarcomas exhibited a wide spectrum of differentiation and could be recognized readily as tumors of low-grade or high-grade malignancy on histologic grounds. Satisfactory histologic material was available for retrospective grading in 87 cases. No attempt was made to grade rhabdomyosarcomas and syno-

TABLE 3. *Relationship of Histologic Grading of Malignancy and Size of Tumor to Survival (Fibrosarcoma and Liposarcoma Only)*

Tumor Size	High Grade Tumors #	High Grade Tumors 5-Year Survival	Low Grade Tumors #	Low Grade Tumors 5-Year Survival
>5 cm	18	33%	38	58%
<5 cm	8	63%	9	88%
Not documented	13	—	11	—
Total	39	46%*	58	74%*

*$X^2=6.67$; $P<0.01$

vial sarcomas and other types which in general do not show such a wide spectrum of differentiation.

Of the graded tumors, 39 were of high-grade while 58 were of low-grade malignancy (Table 3). The 5-year survival rates were 46% and 74% respectively, indicating a positive correlation between high tissue grade of malignancy and poor prognosis. Tumor size did not bias the comparison. In fact, there were fewer large tumors in the high-grade group than in the low-grade group. The additive adverse influence of large tumor size and high tissue grade is however obvious; only 6 of 18 cases in this category survived 5 years (33%). By contrast 8 of 9 patients who had small tumors of low tissue grade survived (88%).

Surgical Treatment and Results

One-hundred fifty-eight patients underwent soft part resections while 139 had major amputations or disarticulations. Tables 4 and 5 give the 5-and ten-year survival rates of these patients according to anatomical location of the sarcoma. The overall 5-year survival rate for soft part resection was 63%, while that for limb exarticulation was 45%. The two groups of patients are not comparable, however. Tumors which were small and favorably situated tended to be treated by soft part resection. On the other hand, large tumors, frequently invading bone, joint, or major neurovascular structures, required amputation, because it was felt to be the only feasible method of extirpation with a good margin. Thus, 66% of the soft part resection group had large tumors compared to 94% in the amputation group. Histologic type and tissue grade of malignancy were comparable in the two groups. Tumor size therefore appears to be one factor responsible for better cure rates observed after soft part resections.

The 10-year survival rate of the whole series was 41%. It was 50% for the soft part resections and 29% for amputations. The greatest number of deaths occurred during the first two years after surgical treatment. Beyond this period, a slower rate of attrition was observed. A few patients succumbed to metastatic sarcoma developing as late as 15 years after curative surgical treatment.

Local Recurrence

Local recurrence of sarcoma occurred in 18% of the series (Table 6). For previously untreated sarcomas, the local recurrence rate was 12%. Of the previously treated cases, 26% developed local recurrences after therapy at our Center. Local recurrence was more common after soft part resections (28%) compared to recurrence on or adjacent to amputation stumps (7%).

The anatomic location of the sarcoma appeared to have an important bearing on the risk of developing a local recurrence. Local recurrence was most frequent with tumors of the leg, occurring in 36% of those treated by soft part resection. The majority of these tumors arose in the popliteal fossa or otherwise in areas adjacent to the knee joint. Eighteen per cent of the tumors situated in the thigh developed local recurrence. The majority of these were tumors situated at or near the groin, or were otherwise closely related to the femoral vessels.

Local recurrence did not occur after amputation or disarticulation for sarcomas of the leg and foot, but it developed in 10 of the thigh cases. Five of these sarcomas had been treated by hip joint disarticulation, and the other 5 by hemipelvectomy. The majority of these tumors were located proximally in the thigh and many were actually at the groin. It was probably difficult in these cases to obtain a wide margin of resection. Data on the size of the tumor and the histologic grading were insufficient to permit a meaningful analysis of their influence on the frequency of local recurrences.

Treatment of Local Recurrences and Outcome

Of the 54 patients who developed local recurrence, 8 were found to have distant metastases at the same time and were treated palliatively. Treatment was not given to or refused by three patients. Radiation therapy was offered as the sole treatment of recurrent sarcoma in 7

TABLE 4. *5-Year Survival Free of Disease After Surgical Treatment*

	Thigh	Leg	Foot	All Sites	
Soft Part Resections:					
1. Previously untreated cases	46/71	15/21	2/2	63/94	67%
2. Previously treated	22/44	14/18	1/2	37/64	58%
Overall	68/115	29/39	3/4	100/158	63%
Amputations:					
1. Previously untreated cases	14/48	5/10	6/9	35/67	52%
2. Previously treated	20/58	5/11	3/3	28/72	39%
Overall	44/106	10/21	9/12	63/139	45%
All Cases	112/221 (51%)	39/60 (65%)	12/16 (75%)	163/297	55%

TABLE 5. *10-Year Survival Free of Disease After Surgical Treatment*

	Thigh	Leg	Foot	All Sites
Soft Part Resections				
1. Previously untreated cases	32/58	6/14	2/2	40/74 (54%)
2. Previously treated cases	14/38	10/15	——	24/53 (45%)
Overall.	46/96	16/29	2/2	64/127 (50%)
Amputations				
1. Previously untreated cases	8/35	2/7	3/7	13/49 (27%)
2. Previously treated cases	13/47	2/5	2/2	17/54 (32%)
Overall	21/82	4/12	5/9	30/103 (29%)
All Cases	67/178 (38%)	20/41 (49%)	7/11 (64%)	94/230 (41%)

instances; one patient survived 4 years with partial control of disease. Table 7 shows the treatment and results in the remaining 35 patients. Twenty-two patients had soft part resection of the recurrent sarcoma resulting in control of the disease in 4 cases, further local recurrences in 10 cases, and an additional salvage of 4 patients after further soft part resection or amputation. Thirteen patients were subjected to amputation as curative treatment for a first or subsequent local recurrence, with eight survivors. The overall salvage rate after the occurrence of locally recurrent sarcoma was therefore 30% (16 of 53) for the whole group, and 46% (7 of 25) for the surgically treated cases. Treatment of local recurrence was eminently successful by amputation which yielded 11 of the 16 survivors.

Tumors Invading Major Blood Vessels or Nerves or Bone

Tumor was found to be intimately related to bone or major neurovascular structures in 62 cases. Amputation was performed or advised in most of these instances, but many pateints refused this form of treatment. The overall five year survival rate for this group of patients was 45%. Thirty-nine amputations and 23 soft part resections were done, with corresponding survival rates of 38% and 48%. These figures are not significantly different from those of cases free from such involvement.

Of particular interest are 6 cases in which en bloc soft part resection was performed with excision of portions of the femoral vessels (4 cases), femur (one case) and the sciatic nerve (one case). Four of these patients survived free of disease for over 10 years. Two died of disease at 3 and 5 years respectively (Table 8).

Metastases to Inguinal Lymph Nodes

Eleven patients had histologically confirmed metastases of sarcoma to the inguinal lymph nodes: synovial sarcoma, 4 cases; rhabdomyosarcoma, 4 cases; leiomyosarcoma, one case; fibrosarcoma, one case; and giant and spingle cell sarcoma, one case. Nodal metastases of liposarcoma was not encountered in this series. Inguinal node dissection was performed as a part of the soft part resection for many tumors of the thigh. Elective inguinal dissections, however, were carried out mainly for suspiciously enlarged nodes, particularly for synovial sarcomas and rhabdomyosarcomas. Only two of the 11 patients with lymph node metastases survived without evidence of disease for 5 years.

Distant Metastases

Distant metastases were the direct cause of death in 90% of the cases. Pulmonary metastases, either solitary or multiple, were by far the commonest. Next in frequency were multiple metastases in different organs and tissues, almost always including the lungs or the pleura. In fact, more than 80% of the patients who died had clinical or radiographic manifestations of pulmonary or pleural metastases. Less common were metastases to bones, intra-abdominal organs, the retroperitoneum, central nervous system, and soft somatic tissues, in that order.

Time of Occurrence of Local Recurrence and Metastases

Table 9 shows the time of occurrence of recurrent sarcoma, local or distant, or both, after "definitive"

TABLE 6. *Local Recurrence After Surgical Treatment*

	Thigh	Leg	Foot	Frequency of Local Recurrence All Sites
Soft Part Resections				
1. Previously untreated cases	11/71	5/21	0/2	17%
2. Previously treated cases	19/44	9/18	0/2	44%
Overall	30/115	14/39	0/4	28%
Amputations				
1. Previously untreated cases	3/48	0/10	0/9	4%
2. Previously treated cases	7/58	0/11	0/3	10%
Overall	10/106	0/21	0/12	7%
All Cases	40/221	14/60	0/16	54/297 (18%)

TABLE 7. *Curative Treatment and Survival After Local Recurrence of Sarcoma*

	Thigh		Leg		All Sites	
	#	5-Year Survivors	#	5-Year Survivors	#	5-Year Survivors
Curative Surgical Treatment of Recurrent Sarcoma						
1. Soft part resection	10	4	2	0	12	4
2. Soft part resections, 2 or more	3	1			3	1
3. Soft part resection, subsequent amputation	5	3	2	0	7	3
4. Amputation	4	1	9	7	13	8
Total	22	9	13	7	35	16 (45%)

surgical treatment. Fifty per cent of the recurrences developed within the first 12 months, while 80% were within 24 months. The frequency dropped abruptly after the end of the second year, but a few distant metastases did appear as late as 10 to 15 years after treatment.

Adjunctive Radiation Therapy

Radiation therapy was employed as an adjunctive to curative surgery in 18 cases: preoperatively in 7 instances and postoperatively in 11. There were 10 liposarcomas in this group of which 7 survived 5 years. Of 8 patients with other sarcomas, only 2 survived. These numbers are too small for meaningful analysis.

Discussion

Major amputation or disarticulation offers the surest means of eradication of a soft tissue sarcoma in terms of obtaining the widest margin of resection. However, the clinician's choice of treatment by exarticulation must be tempered by two factors; firstly, the permanent loss of an extremity, and secondly, the risk of treatment failure due to the development of distant metastases. The present series shows that this risk is greater than 50% (Tables 5 and 6). As an alternative, local, non-amputative surgical treatment is notorious for its high frequency of local recurrence, from 30% to over 60%, according to various reports.[1,4,5,10,14] Recognizing this, Bowden and Booher formulated in 1958 the principles and technique of adequate soft part resection for sarcoma,[3] which have since been employed at our institution. From a theoretical standpoint, such a monobloc resection, tailored to the topography of the tumor-bearing site, and widely encompassing the confines of the tumor, should yield results at least as good as those of an amputation. Retrospective examination of cases in this series, though admittedly subject to criticism because of biases in the treatment groups, does indicate that the 5-year survival rate of 63% not only equaled, but also surpassed that of the amputation group.

A premium must be paid, however, for preserving the extremity. The present series records a local recurrence rate of 28% (17% for previously untreated cases), after soft part resections, compared to 7% for amputations. These local failures were most common with tumors in the groin or the popliteal fossa. Here, the proximity of major blood vessels, nerves, bones, or joints, militate against proper execution of a true monobloc resection with adequate margins of normal univolved tissues. Interestingly, the occurrence of local recurrence was not synonymous with a fatal outcome. In fact, at least 30% of these patients were salvaged by further aggressive surgical measures, and in the absence of distant metastases, secondary treatment by amputation gave a salvage rate of 55%.

The factors which apparently influenced the frequency of distant dissemination of a sarcoma are the histologic type, the grade of malignancy and its size. Inasmuch as these discriminating forces seemed to exert their effects equally on the patients irrespective of whether they were treated by amputation or soft part resection, the less

TABLE 8. *Soft Part Resection With En Bloc Excision of Major Nerve, Bone or Blood Vessels*

Patient	Location of Tumor	Histology	Structures Removed	Status
G. A.	Thigh	Synovial sarcoma	Sciatic nerve	Alive 10 yrs, NED
F. R.	Thigh	Malignant schwannoma	Superficial femoral vein, Profunda artery and vein.	Alive 10 yrs, NED
A. H.	Thigh	Fibrosarcoma	Femur	Hemipelvectomy for local recurrence, alive 15 yrs, NED
J. S.	Thigh	Liposarcoma	Superficial femoral artery and vein	Alive 10 yrs, NED
M. B.	Thigh	Rhabdomyosarcoma	Superficial femoral artery and vein	Died of disease 6 yrs
G. W.	Thigh	Liposarcoma	Femoral artery	Died of disease 3 yrs

TABLE 9. *Time of Occurrence of Local Recurrence or Distant Metastases*

Onset (months)	Local Recurrence and/or Distant Metastases	Number of Cases With Pulmonary or Pleural Involvement
1-12	54	40
13-24	33	25
25-36	7	4
37-48	8	4
Over 48	6	5

mutilating procedure should always be the first choice in a given case. Technical factors must dictate which sarcoma should be treated by limb disarticulation. Extensive involvement of bone and proximity to a joint can be indications for amputation. Amputation is also advisable for local recurrence of sarcoma after a genuine effort at wide monobloc resection as defined above. Proximity or involvement of the femoral artery and vein need not be a deterrent to an adequate soft part resection. Frequently, more than one tissue plane separates the tumor from the vessels. If a good margin cannot be obtained, the femoral vessels can be excised en bloc as in several cases in the present series. Recently, we have successfully performed arterial and vein grafting procedures in such circumstances, using a Dacron prosthesis and the saphenous vein from the opposite thigh to replace the respective vessels.

High dose intra-operative isolation-perfusion chemotherapy of the tumor bed and adjunctive radiation therapy are two methods which may be used with the hope of reducing the risk of local recurrence. The former was not employed in this series. Only a small number of cases received adjunctive irradiation, so that its possible benefit could not be evaluated. Previous experience indicates that in general the radiosensitivity of sarcomas are unpredictable,[9] although radiation therapy is more likely to be effective with liposarcomas.[11,13]

More than half of these patients ultimately succumbed to distant metastases of sarcoma. Occult foci of sarcoma must be present at distant sites during or soon after eradication of the primary tumor. Under the premise that such small numbers of neoplastic cells are likely to be most sensitive to chemotherapy, we have recently instituted prophylactic postoperative treatment of these patients with chemotherapeutic agents known to be relatively effective against sarcoma. The recent demonstration of sarcoma associated antigens and host immune response to cell-surface antigen in human sarcomas[7,15] suggests the possibility of immuno-therapeutic manipulations in this disease. It is hoped that these newer approaches to treatment will materially increase the salvage rate of these patients in the near future.

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Adenyl Cyclase*

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Many hormones interact with their target cells by binding to receptors located on the external surface of the target cells' plasma membrane and subsequently stimulating the enzyme, adenyl cyclase, which is located within the plasma membrane. Stimulation of adenyl cyclase results in formation of cyclic AMP which is released from the membrane into the cell and acts within the cell to regulate a wide variety of cellular processes. In this review, the characteristics of hormone receptors and the relationship between receptor occupancy and adenyl cyclase stimulation are discussed. Our current understanding of the roles of hormones, substrate, magnesium, calcium, and guanine nucleotides as regulators of adenyl cyclase activity is summarized. Because of the central importance of adenyl cyclase and cyclic AMP as mediators of the cellular response to hormones, it is to be expected that many diseases may result from defects in this enzyme system. Indeed, several adenyl cyclase related diseases have been identified and the molecular bases for these diseases are discussed in this review.

ADENYL CYCLASE is an enzyme which is found in the plasma membrane of a wide variety of cells. This enzyme catalyzes the conversion of ATP to cyclic AMP and pyrophosphate (Fig. 1). An extremely important feature of the enzyme, adenyl cyclase, is its ability to be stimulated by a wide variety of hormones. In fact, adenyl cyclase was the first enzyme discovered to be capable of being stimulated by hormones. It now appears that the basis for the effect of many hormones on their respective target cells is the stimulation of the target cell adenyl cyclase by these circulating hormones and the subsequent accumulation of cyclic AMP within the target cell.

In this selective review, some of the information which describes the characteristics of adenyl cyclase and the stimulation of adenyl cyclase by hormones will be summarized. In addition, there will be a brief discussion of the molecular basis for some diseases which result from abnormalities of the adenyl cyclase system. This review is intended to provide a general background in this important area of biochemistry which will facilitate the critical evaluation of new "cyclic AMP" data. Although general concepts are stressed, there will be included references to many of the original investigative reports in which the reader may find detailed presentations of experimental methods and techniques.

Cyclic AMP—The Second Messenger

Hormones elaborated by endocrine cells are released into the circulating blood. Steroid hormones, such as the estrogens and androgens, appear to penetrate their target cells, bind to receptor proteins in the cytoplasm, and only then to alter target cell activity.[32] However, a large number of non-steroid hormones affect their target cells without penetrating the target cell plasma membrane. Among this latter group of hormones are included the catecholamines as well as many peptide hormones such as ACTH, TSH, secretin, glucagon, parathormone and calcitonin.[3,46] These peptide and catecholamine hormones bind to receptor proteins located on the external surface of the target cell plasma membrane.

In 1958, Sutherland and co-workers discovered cyclic AMP and shortly thereafter adenyl cyclase.[54] These workers proposed the "second messenger" concept to explain how hormones, binding to the external surface of the target cell plasma membrane, might effect a cellular response.[55] According to this concept, the circulating hormone is termed the "first messenger." When this first

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*The correct name of this enzyme is adenylyl cyclase (ATP: pyrophosphate-lyase (cyclizing), EC 4.6.1.1) which is based on the actual chemical reaction that it catalyzes. It has also been referred to as adenylate cyclase. In this review it will be referred to as adenyl cyclase because it is more commonly referred to in this way, was so named by its discoverers, and is easier to say.[46]

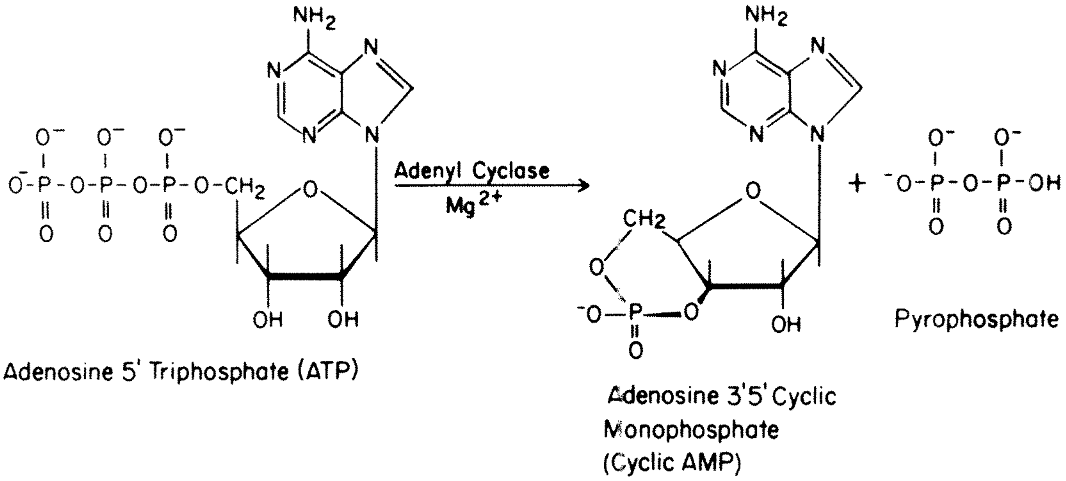
Adenyl Cyclase
Mg^{2+}
Adenosine 5' Triphosphate (ATP)
Adenosine 3'5' Cyclic Monophosphate (Cyclic AMP)
Pyrophosphate

FIG. 1. Formation of cyclic AMP from ATP.

messenger binds to its receptor, the adenyl cyclase in the plasma membrane is stimulated and ATP is converted into cyclic AMP (Fig. 2). The newly formed cyclic AMP is released from the internal surface of the plasma membrane into the cytoplasm. The cyclic AMP is termed the "second messenger" because it moves from the plasma membrane into the cell. Eventually, the cyclic AMP itself binds to proteins known as protein kinases which are in the cytoplasm. These protein kinases become activated upon binding cyclic AMP and the activated protein kinases stimulate or inhibit various metabolic reactions. This, in turn, leads to a specific cellular response which, depending upon the cell, may involve changes in enzyme secretion, ion transport, muscle contraction, hormone synthesis, etc.[48] Eventually, the second messenger cyclic AMP is metabolized to 5′ adenosine monophosphate (5′ AMP) by the enzyme cyclic nucleotide phosphodiesterase, and the stimulus of the "second messenger" is dissipated (Fig. 2).

Hormone Specificity

The cellular response to hormonal stimulation is highly specific. For example, the catecholamine hormones affect only certain cell types and not all cell types affected by the catecholamines respond in the same way. This specificity in response may be explained by three variables: 1) the hormone receptors; 2) the second messenger; and 3) the protein kinases.

1) Hormone receptors convey specificity in several ways. Only those cells possessing the proper receptors are capable of binding a given circulating hormone. In addition, whether the receptors will or will not be occupied by the hormone is determined both by the circulating hormone concentration and by the affinity of the receptors for that hormone according to the following equilibrium expression: $K_a\,[H] = \frac{[RH]}{[R]}$ where K_a is the affinity constant of the receptor for the hormone, [H] is the unbound hormone concentration, and $\frac{[RH]}{[R]}$ is the ratio of the concentrations of occupied ([RH]) to vacant ([R]) receptors. Because receptors for a given hormone may have varying affinity constants from cell type to cell type, at any particular circulating hormone concentration differing cell types may have differing degrees of receptor occupancy.

2) Although the quantitative extent of receptor occupancy by a hormone may determine the *magnitude* of the cellular response to the circulating hormone, it does not determine the *nature* of that response. The events which follow hormone binding determine the nature of the cellular response. Binding of catecholamines to the β-adrenergic receptor or binding of many peptide hormones to their respective receptors (Table 1) results in stimulation of adenyl cyclase.[48] On the other hand, occupancy of other hormone receptor types, such as those for insulin and the α-adrenergic receptors,[55] does not result in adenyl cyclase stimulation. The pathway by which adenyl cyclase is stimulated and the function of its "second messenger" cyclic AMP within the cell has been outlined above. There is now evidence of other "second messengers" which mediate the effects of hormones which bind to cell surface receptors but do not stimulate adenyl cyclase. These other "second messengers" include cyclic guanosine monophosphate (cyclic GMP)[25] and ionized calcium.[47] They will not be discussed further in this review.

3) Specificity in the cellular response to a circulating hormone is determined by the particular protein kinases in a given cell which eventually bind the "second messenger" and the cell processes which are altered by these protein kinases. For example, both liver and fat cells each have cyclic AMP dependent protein kinases which bind cyclic AMP. While each cell type responds to β-adrenergic stimulation by activation of adenyl cyclase and formation of cyclic AMP, the effect of cyclic AMP in the liver cell is to accelerate glycogen breakdown,[29,48] while in the fat cell cyclic AMP causes an acceleration of

lipolysis.[29,48] This difference in cellular response occurs because the liver and fat cells contain different types of cyclic AMP dependent protein kinases and, in each cell type, different metabolic processes (i.e., enzyme catalyzed reaction pathways) are affected by the activated cyclic AMP dependent protein kinases.

The Regulation of Adenyl Cyclase Activity

The rate at which a substrate is converted into a product by an enzymatically catalyzed reaction is a measure of the catalytic rate for that enzyme under those conditions. One general feature of enzymes which catalyze reactions at key points along metabolic pathways is the ability of that enzyme to manifest differing catalytic rates.[24,43] Substances called "regulatory agents" may either increase or decrease the catalytic rate of the enzyme under those conditions. The catalytic rate which occurs when no stimulating agents are present is called the basal activity. Regulatory agents may alter the activity of an enzyme by either stimulating or inhibiting it. In addition, there may be an interaction between various regulatory agents (e.g., antagonism, synergism, additivity) such that one agent may alter the response of an enzyme to another agent.

Adenyl cyclase is an enzyme whose activity may be altered by regulatory agents. Since cyclic AMP plays a central role in controlling many cellular functions, we must achieve an understanding of the agents and mechanisms which regulate the activity of adenyl cyclase.

A hormone which stimulates adenyl cyclase may be considered a regulatory agent because it alters the activity of the enzyme. The hormone causes this stimulation after first binding to the hormone receptor. Similarly, ATP which is the substrate for the adenyl cyclase catalyzed reaction, and which binds to the "active" or "catalytic" site on the enzyme, may alter enzymatic activity because the concentration of ATP available to the adenyl cyclase will limit and determine the rate at which product may be formed.

In addition to the hormone and the substrate, other substances are capable of altering the activity of adenyl cyclase. In order to regulate the activity of adenyl cyclase, these substances (to be discussed shortly) must first interact with the enzyme. The location of this point of interaction is termed the "binding site" for that regulatory agent. Regulatory binding sites are either part of or coupled to the adenyl cyclase. For reasons of clarity, I have chosen to assume that all of the various regulatory binding sites are part of one macromolecular complex (Fig. 2) which also includes a hormone receptor and the substrate binding site. It should be emphasized that this may, in fact, be an oversimplification. It may be found, for example, that one or more of these binding sites is located at a point distant from the catalytic site of the enzyme and that the interaction between these various areas reflects a generalized or localized change in the membrane matrix which allows for the transfer of an effect from a binding site on one macromolecule to the catalytic site located on another macromolecule.[46] The eventual activity of the enzyme, however, is determined by a summation of the effects of all of the stimulatory and inhibitory agents which interact either directly or indirectly with the adenyl cyclase.

We will discuss the regulation of adenyl cyclase activity by 1) hormones, 2) substrate, 3) cations, 4) nucleotides and 5) prostaglandins. Each of these regulatory agents interacts with its own binding site and the characteristics of these binding sites may, to a great extent, define the characteristics and properties of the adenyl cyclase system.

1) *Hormone Receptors.* The exact chemical and struc-

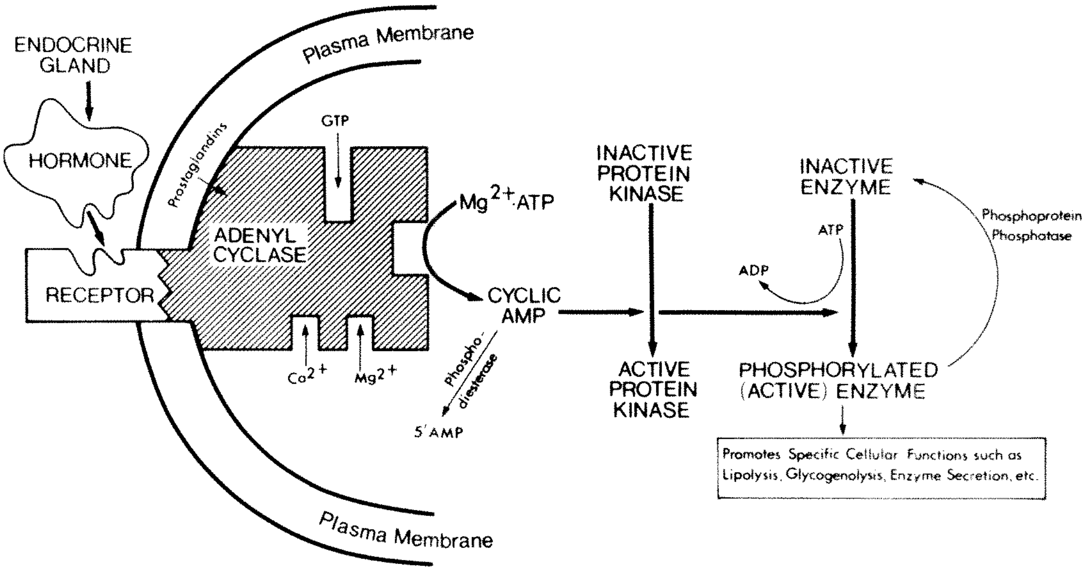

FIG. 2. The adenyl cyclase system.

TABLE 1. *Hormones Which Stimulate Adenyl Cyclase*

Glucagon	ACTH
Vasopressin	TSH
Parathormone	LH
Triiodothyronine	FSH
Prostaglandins	Dopamine
Secretin	Norepinephrine
Hypothalamic Releasing Factors	Epinephrine
MSH	Thyrocalcitonin
Serotonin	Histamine

tural nature of hormone receptors is unknown. Receptors for many hormones are believed to be, at least partly, composed of proteins.[18] As mentioned earlier, the receptors for steroid hormones are located within the cytoplasm of the target cell whereas the receptors for most peptide and catecholamine hormones are located on the outer surface of the target cell plasma membrane. It is likely that the structure of the receptor determines the hormone structure which is most favorable for binding (i.e., the size, shape, hydrophobicity, and ionic character which will best fit the receptor). Thus, departures from the structure of naturally occurring peptide hormones or catecholamines may increase or decrease the tightness of binding to the cell surface receptors for that particular hormone. This aspect of hormone specificity is most clearly seen in the case of the catecholamine receptors which have actually been divided into classes and subclasses on the basis of the hormone structures which are most tightly bound. Thus, the α-adrenergic receptors bind the catecholamines in the following order of affinity: phenylephrine > epinephrine = norepinephrine > isoproterenol. The β-adrenergic receptors bind the catecholamines in the following order: isoproterenol > norepinephrine = epinephrine > phenylephrine.[23] Moreover, only the 1-stereoisomers of the hormones are bound.[1,20] Similarly, the structure of the blocking agents determines their specificity. For example, propranolol and practolol block only the β-adrenergic receptors whereas phenoxybenzamine and dibenzyline block only the α-adrenergic receptors.[23]

Some of the hormones which have been found capable of stimulating adenyl cyclase are shown in Table 1. It appears that β-adrenergic receptor binding, but not α-adrenergic receptor binding, is coupled to adenyl cyclase stimulation.[48] Many target cells possess receptors for more than one type of hormone. For example, the fat cell binds glucagon, secretin, ACTH, and catecholamines and each of these hormones causes stimulation of fat cell adenyl cyclase.[6] Early studies showed that when combinations of these hormones were present at saturating concentrations, the activity of adenyl cyclase was less than the sum of the activities elicited when each of these hormones was present alone.[4] This suggested that the different types of hormone receptors were all coupled to the same enzyme unit. More recently, however, it has been shown that additivity in hormone response can be elicited under certain conditions and that the characteristics of adenyl cyclase response varies from hormone to hormone. This suggests that, in fact, the various types of hormone receptors may be linked to different types of adenyl cyclase.[50] Proof of this, however, must await further experimentation.

Little is known of the number and density of hormone receptors on most target cell surfaces. However, in one situation, the turkey erythrocyte, each cell was found to possess 600-1000 β-adrenergic receptors with an average receptor density of 1-2 per μm^2.[37] Whether or not these receptors are randomly distributed across the cell surface or exist in clusters is unknown. Similarly, it is not known whether receptors for hormones on other cell surfaces are more or less numerous.

A variety of experimental reports have suggested that the hormone receptors face outward from the cell surface and that the adenyl cyclase faces inward toward the cytoplasm of the cell.[3] We have very little understanding of the molecular events which couple hormone binding to adenyl cyclase activation. There is circumstantial evidence suggesting that phospholipids participate in this process. For example, although a detergent extract of myocardial tissue did not show adenyl cyclase activity in the presence of hormones, restoration of the response to specific hormones could be obtained by the addition of specific phospholipids.[38-41] As we shall see later, there is also evidence suggesting that guanyl nucleotides participate in the coupling between hormone receptor binding and adenyl cyclase activation.

2) *The Adenyl Cyclase Catalytic Site.* As mentioned previously, adenyl cyclase activity has been detected in a large variety of cell types from all animal phyla, and, in addition, in bacteria and fungi.[48] At the present time, only bacterial adenyl cyclase has been isolated in a pure state.[56] Bacterial adenyl cyclase, however, is not responsive to hormone stimulation. When adenyl cyclase from higher animal forms is purified, we may then discuss the catalytic component in molecular terms and define the similarities and differences between adenyl cyclases in differing cell types in terms of their actual structure. At the present time, we may only compare the characteristics of adenyl cyclase activity in different cell types. The apparent affinity for ATP is similar for the adenyl cyclase from a large variety of cell types and is usually between 8×10^{-5} and 5×10^{-4} M.[46] In addition, the pH optimum is usually close to pH 7.4.[46] There is now strongly suggestive evidence that the actual substrate for the enzyme is, more specifically, the protonated magnesium—ATP complex (Mg^{2+}-H ATP) and that the unprotonated form of ATP as well as ATP not complexed to Mg^{2+} may inhibit the enzyme.[50] It has been suggested that these inhibitory forms of ATP compete with the protonated

magnesium-ATP complex for binding at the catalytic site and that this explains their ability to inhibit the enzyme.[50] This may be of physiological importance because variations in the levels of cellular ATP, pH and Mg^{2+} would directly affect adenyl cyclase activity.

3) *The Role of Cations*. The adenyl cyclase from most cell types appears to possess regulatory binding sites for the cations of magnesium and calcium. Magnesium acts in two ways. It binds to ATP to form the substrate which is the protonated magnesium-ATP complex.[50] In addition, magnesium binds to one or more regulatory sites on the enzyme and the occupancy of these regulatory sites by magnesium is required for adenyl cyclase activity.[4,52]

Ionized calcium has been found to inhibit the adenyl cyclase in most cell types. In one case, the inhibitory effect of calcium was shown to result from the binding of calcium to a cluster of specific calcium binding sites.[52] It has been suggested that the regulation of adenyl cyclase by calcium may be physiologically important in many types of cells.[53]

4) *Nucleotides*. The adenyl cyclase from a variety of cell types has now been shown to be stimulated by guanyl nucleotides such as guanosine triphosphate (GTP) and the GTP analog 5′-guanylyl-imidodiphosphate ($G_{pp}(NH)_p$).[2,15,34,36,57] In addition, these nucleotides appear to enhance the stimulatory effect of hormones.[2,35,36,57] In fact, the effect of glucagon in stimulating liver adenyl cyclase has been shown to require the presence of guanyl nucleotides.[49] This has prompted the suggestion that the direct stimulator of adenyl cyclase in this instance is not the hormone but is GTP.[50] In any event, it appears that these nucleotides may be important physiological regulators of adenyl cyclase.

5) *Prostaglandins*. The prostaglandins are a group of 20-carbon fatty acids synthesized within many cell membranes that appear to be intrinsic regulators of adenyl cyclase for that particular cell. A variety of prostaglandins have now been identified and in some tissues the different prostaglandins may have differing effects on the adenyl cyclase. For example, prostaglandin E_1 elevates platelet cyclic AMP while prostaglandin E_2 lowers platelet cyclic AMP levels.[51] As with the other regulators of adenyl cyclase activity, the prostaglandins probably act by binding to regulatory sites but the mechanism of their effect is not known.

Fluoride

The fluoride ion has been found to stimulate adenyl cyclase activity in broken cell preparations from a wide variety of tissues.[46] For the most part, however, fluoride does not stimulate adenyl cyclase in intact cells. In broken cells, relatively high fluoride concentrations are required (1×10^{-2} M) for stimulation. The mechanism of this "fluoride effect" is not known but it has been suggested that fluoride works by eliminating pre-existing inhibitory forces which may be present.[14]

Adenyl Cyclase and Disease

We may now look upon the adenyl cyclase system as one consisting of many components (Fig. 1): 1) hormone receptors binding specific hormones; 2) adenyl cyclase catalytic unit catalyzing the formation of cyclic AMP; 3) regulatory sites altering the response of the catalytic unit to stimulation; 4) cyclic AMP dependent protein kinases binding cyclic AMP and thereby becoming converted from inactive to active protein kinases; 5) intracellular enzymes which are activated or inhibited when they are phosphorylated by the activated cyclic AMP dependent protein kinases; 6) phosphoprotein phosphatases which dephosphorylate the intracellular enzyme systems which were phosphorylated by the cyclic AMP dependent protein kinases; 7) cyclic nucleotide phosphodiesterase which breaks down cyclic AMP by converting it to 5′ adenosine monophosphate. Adenyl cyclase related diseases may represent changes in one or more components of this system. At the present time, only a few diseases have been proven to be related to the adenyl cyclase system.

Cholera

The *Vibrio comma* which causes cholera elaborates a toxin which binds to substances called gangliosides in the plasma membrane of many types of cells.[16,17,19] Cholera toxin, by binding to intestinal cells, activates adenyl cyclase and causes an increase in intestinal cell cyclic AMP levels. This results in net fluid and electrolyte secretion rather than absorption by the intestine[31] and causes the profound diarrhea which is found in the disease cholera.

Pseudohypoparathyroidism

In pseudohypoparathyroidism, normal or elevated parathormone levels are found in the circulating blood but the end organs (kidneys and bone) fail to respond.[13] Normally, parathormone stimulates cyclic AMP production in renal cortical cells and osteoclasts in bone resulting in phosphate excretion from the kidney and resorption and calcium liberation from bone.[10–12,44] In pseudohypoparathyroidism, both of these responses are lacking. It has been suggested that either the hormone receptors or the enzyme itself is defective in this disease.

Nephrogenic Diabetes Insipidus

Normally, antidiuretic hormone (ADH) stimulates the adenyl cyclase in cells of the distal collecting tubule of the kidney and elevated cyclic AMP levels cause an increased permeability of these cells to water which then passes out of the collecting tubules into the hypertonic renal medulla and leads to concentration of the urine.[9,11,26,45] There is a type of nephrogenic diabetes insipidus which appears to be genetically transmitted. These patients have normal or elevated circulating levels of ADH but the cells of the distal collecting tubule do not respond.[22] It is not known, at present, which of the elements of the adenyl cyclase system is defective in this disease.

Glycogen Storage Diseases

The adenyl cyclase system plays a central role in regulating glycogen metabolism because glycogen breakdown (by the enzyme glycogen phosphorylase) is stimulated by cyclic AMP and glycogen synthesis (by the enzyme glycogen synthetase) is inhibited by cyclic AMP.[48] At least 2 forms of glycogen storage disease have now been identified which appear to represent defects in the adenyl cyclase system because of the absence of specific key enzymes. McArdle's disease results from an absence of muscle glycogen phosphorylase[21,42] and Hers' disease is caused by a deficiency of liver glycogen phosphorylase.[28,30]

Suspected Adenyl Cyclase Diseases

It is now recognized that the adenyl cyclase system is an extremely important element in a large number of cells. In essence, it represents the receiver and amplifier for effecting the cellular response to many hormones. It will, therefore, not be surprising if defects of this system are found to be the basis for many common diseases. Indeed, there is evidence to suggest that some forms of hypertension, diabetes and obesity may result from defects in the adenyl cyclase system. It would seem appropriate at this time to define the criteria which should be met before a disease or physiological process is accepted as involving the adenyl cyclase system.

If a physiological process is mediated by cyclic AMP, one should be able to demonstrate cyclic AMP formation in the relevant cell type in the presence of the appropriate hormone but not in the absence of that hormone. In addition, the physiological process should be observed when the cell is exposed to cyclic AMP or one of its derivatives such as dibutyryl cyclic AMP and this effect may be enhanced when cyclic nucleotide phosphodiesterase inhibitors such as theophylline are also present. In addition, the physiological response after hormone stimulation should occur coincident with or following the observed elevation in cyclic AMP.[55] It should be emphasized, however, that experiments such as those outlined above should be done under physiological conditions with appropriate concentrations of hormones, substrate and cations.

Similar considerations should be applied in the design of experiments linking diseases to the adenyl cyclase system. In this case, however, one must demonstrate that the physiologically involved hormone is present in normal concentrations at the cell surface and that this hormone is structurally normal itself. The lack of the normal physiological response, then, would represent a failure of some element of the adenyl cyclase system to respond to the hormone.

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Distal Antrectomy With Vagectomy for Duodenal Ulcer:

Results in 611 Cases

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Distal antrectomy (25% or less) resection of the distal stomach with bilateral vagectomy, Billroth II, antecolic, Polya or Hofmeister gastrojejunostomy, continues to be our operation of choice for chronic duodenal ulcer. This is based upon our experience in 611 operations and as a result of careful complete repeat in-patient followup studies conducted since our original operation which was devised and performed in July 1953. This procedure controls or eliminates the two major gastric acid stimulatory phases responsible in the pathogenesis and chronicity of a duodenal ulcer: neurogenic (cephalic phase) via the vagal gastric pathways, and the humoral (gastrin) phase via antral stimulation. Even though part of the antrum may remain in the gastric remnant in some patients, antral control is maintained because the antrum remains in the gastric acid stream, there is no stasis, and it is vagectomized. The ulcer diathesis is controlled with a minimal disturbance in gastric physiology, in function, and in gastric reservoir capacity; the procedure will almost eliminate all of the undesirable postoperative gastrointestinal sequelae associated with other operations for duodenal ulcer. It insures the least chance for marginal, gastric, or recurrent ulcer formation, and a low morbidity rate.

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THE PATHOGENESIS of a duodenal ulcer is now understood due to the investigational studies conducted by L. R. Dragstedt and his associates and several other investigators in various centers throughout the world.[1-16] The two gastric secretory phases responsible for the major production of free hydrochloric acid and pepsin are the neurogenic and humoral.

The neurogenic or cephalic phase is regulated through the vagal supply to the gastric glands in the body and fundus of the stomach. Vagal stimulation is responsible for 45-50% of the total gastric secretory output in the normal person. In those with an ulcer diathesis, this phase becomes hyperactive and may be responsible for 80% of the total secretory output.

The hormone or humoral phase is regulated by the gastric antrum. The liberation of gastrin by the antrum is dependent upon the stimulatory influences resulting from delayed emptying of the stomach, presence of food, chemicals, bile or alkaline juices, hypomotility and distention, and puddling of food. In a normal person, 45% of acid-pepsin production is controlled by this regulatory phase. Any decrease or increase in this mechanism is dependent upon the type of surgical procedure performed for treatment of a duodenal ulcer. Procedures which result in delayed gastric emptying, such as pyloroplasty, gastroenterostomy, Billroth I gastroduodenostomy, would increase the output of gastrin from the retained antrum. This is an important factor in the fairly high recurrence rates of a duodenal ulcer or the development of a marginal or gastric ulcer following such procedures, in spite of a complete vagotomy.

These two important gastric secretory regulatory phases are almost wholly independent; however, they affect each other to some degree. Therefore, in order to adequately control the duodenal ulcer diathesis and to prevent recurrent ulceration and/or stomal or gastric ulcer formation, these two major functions should be controlled or eliminated. Conservation of the entire gastric reservoir capacity, with adequate drainage, is the key to the elimination of most all of the undesirable postoperative gastrointestinal sequelae.

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Purpose

In 1949, we were of the opinion that a minimal gastric resection coupled with vagectomy would encompass the ideal combination to control the ulcer diathesis and possibly eliminate many of the undesirable gastrointestinal sequelae. However, at that time there was incomplete investigational research data concerning the role of the antrum in the pathogenesis of a duodenal ulcer.

By 1953 the reports of L. R. Dragstedt and his associates[2,4,5] on the antral function convinced us that the physiologic basis for this procedure was sound. Therefore, in that same year, we conducted a pilot study in 20 patients upon whom a 25 per cent or less distal resection of the stomach with a bilateral vagectomy and an anterior gastrojejunostomy, Polya or Hofmeister Billroth II was performed. By 1957 the 4-year followup reports and studies were so outstanding that we then adopted it as our operation of choice for duodenal ulcer.

The first 350 operations were performed upon consecutive and unselected adult males.

Statistical analysis and evaluation are important modalities which aid in governing trends, adoption or rejection of procedures; also, the establishment of many facets of surgical attitudes are acquired in this manner. Biomedical statisticians have been and are important members of our medical teams. They have had an excellent influence upon us by aiding in placing our data in proper perspective. In some instances, as related to diseases or surgical procedures, a certain number of cases with an adequate period of followup are required in order to meet the criteria established for proper biomedical interpretation. The number of cases in a series to prove or substantiate facts are variable. In some, a series of 50 cases may be all that is required, whereas in others 200-250 cases are needed.

Even though this is the desired goal, the reports derived from a series can vary considerably from time to time. In the first 114 consecutive and unselected cases, including 23 emergency cases with massive hemorrhage, there were no deaths. Then by January 1961 we had performed 329 operations, including emergency and urgent cases with only two deaths (0.6% mortality). However, when the series had reached 611 cases, there were 14 deaths (2.2%) *from all causes* occurring within 30 postoperative days. These will be discussed more completely later.

The selection of patients for surgical intervention has remained the same throughout this and our other reported studies: hemorrhage, obstruction, pain, intractability, perforation, and recurrent ulceration. This entire program was under the direction of one chief of surgery and his permanent staff, all of whom have applied the same basic indications for patient selection. All other factors concerning pre and postoperative management, operative technique, and all ancillary factors were applied to all patients. The follow-up studies and methods of evaluation have likewise been standardized.

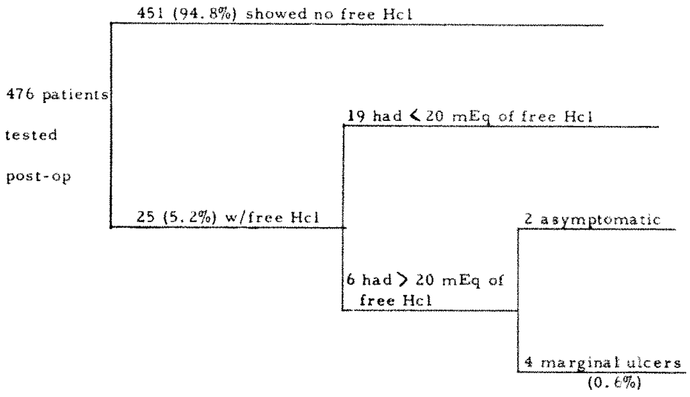
451 (94.8%) showed no free Hcl
476 patients tested post-op
19 had < 20 mEq of free Hcl
25 (5.2%) w/free Hcl
2 asymptomatic
6 had > 20 mEq of free Hcl
4 marginal ulcers (0.6%)

FIG. 1. Gastric analysis.

Followup Program

The patients were contacted at the end of the first 6 months after surgery. If the patient had no complaints or problems, he was contacted at the end of the first year for admission to the hospital for a complete evaluation which included gastric analysis and night secretory volume determination, upper gastrointestinal roentgenographic studies including a motor meal, routine blood and urine examinations, and complete entries in the protocol. This latter covers every phase representing a multipaged review, which allows a thorough evaluation of the patient's status.

The patients were recalled for 3 and 5-year followup examinations, including gastric analysis, routine blood and urine examinations, and every 3 years thereafter.

Age Incidence

The average age was 52.3 years, the youngest was 21, and the oldest 79. The greatest number, 187 (30.6%), were in the 40 to 49-year-old age group; however, 194 (31.7%) were over 60 years of age, and 292 (37.8%) were over 50 years old (Table 1).

Indications for Surgery

A great number of patients had more than one indication for surgery. The most common indications were intractability and bleeding. In both these categories there was considerable overlap. Hemorrhage, in our series, was greater than in many series reported by others. In this group are all patients with a history of bleeding or who were hemorrhaging at the time of admission, at which time definitive surgery was performed.

Preoperative Gastric Analysis

In the first 350 patients, excluding those hemorrhaging at the time of hospitalization or who had pyloric obstruc-

TABLE 1. *Age Distribution.*

Age	Number	Per cent
20-29	29	4.7
30-39	103	16.9
40-49	187	30.6
50-59	98	16.1
60-69	145	23.7
70 and over	49	8.0
Totals	611	100.0

tion, total night gastric secretory volume studies were carried out in addition to free hydrochloric acid determination, after betazole (Histalog) injection and after the Hollander's insulin test. Most patients had 30 or more milliequivalents of free hydrochloric acid in 12-hour night secretions. The average night secretory volume was over 900 cc with a maximum of 3400 cc (Fig. 1).

Type of Operation Performed

The procedure was accomplished through a supraumbilical, elliptical, transverse or right subcostal, oblique transrectus abdominal incision. The bilateral vagectomy was performed after mobilization of the lower esophagus through the esophageal hiatus. The vagus nerves and their branches were completely dissected free for a distance of 3-4 inches along the esophagus down to the stomach. This portion of the vagal pathways was resected. The vagal section, *including all branches, must be complete*. Variations in the branches and pattern of distribution in this area occur and should be known by the surgeon.

TABLE 2. *Complications–Nonfatal–64.*

Intra-abdominal—28 patients (4.7%)	
Abscess	3
Common duct injury	1
Duodenal leak/fistula	11*
Hemorrhage stomal	1
Intraluminal	2
Intraperitoneal	2
Obstruction	4
Pancreatitis	3
Peritonitis	4
	31
Cardiopulmonary—15 patients (2.5%)	
Atelectasis	5
Myocardial infarction	2
Pneumonia	11
Pulmonary infarction	1
	19
Wound—12 patients (2%)	
Dehiscence	4
Hematoma	1
Infection	10
	15
Others—5 patients (0.8%)	
Parotitis	1
Shock	1
Thrombophlebitis, acute	3
	5

*No deaths

A distal antrectomy was performed, removing 25% or less of the distal portion of the stomach. A resection greater than this is not necessary to control antral function and would only decrease the reservoir capacity of the stomach leading to increased incidence and severity of undesirable postoperative gastrointestinal sequelae. The resection was carried distal to the pyloric ring to avoid leaving any antrum in the duodenal stump.

In 53% of the patients, the ulcer was left in situ or on the head of the pancreas. The ulcer was removed in some patients who were hemorrhaging or in whom a safe duodenal closure could not be obtained. The methods of managing the bleeding ulcer site will be discussed later. In recent years, a greater attempt is being made to leave the ulcer in situ, in over 70% of the patients. This reduces the risks and hazards involved in the dissection necessary for resection of the ulcer.

An antecolic gastrojejunal anastomosis, Billroth II, Polya or Hofmeister type, was accomplished, the type depending upon the width of the antral canal. However, no attempt was made to form a small stoma. The afferent jejunal loop was short, 4-5 inches in length. Billroth I performed in carefully selected patients in whom local pathology will not preclude malfunction of a gastroduodenostomy.

The abdominal wounds were closed by approximating the anterior and posterior rectus sheath with fine silk sutures.

The majority of patients were ambulatory on the first day. Nasogastric suction is discontinued as soon as bowel sounds are heard: this usually occurs about the second or third day. Prolonged suction is no longer used even in the presence of delayed gastric emptying. Even though in some patients gastric content is 1,000 cc or more, suction is discontinued. If a patient has distress as a result of overdistention from delayed gastric emptying, intermittent gastric aspiration is performed. With this procedure, prolonged delayed emptying of the gastric remnant has not been a problem. With a more rapid progression and greater liberalization in food intake and with the need of nasogastric suction for only a short period of time, we have not found it advisable or desirable to use gastrostomy. We believe the risks involved are much greater than the program outlined above. In some patients who are properly observed, postoperative nasogastric suction is not necessary.

Longer nasogastric decompression of the stomach is necessary and safe in the elderly, debilitated patient, in the mentally incompetent patient, in the uncooperative

TABLE 3. *Local Management of Duodenal Ulcer (1965 to 1968).*

Age	No.	Resected	Duodenum	Nonresected Situ Pancreas	Transfixed
20-29	4	2	1	1	0
30-39	13	5	6	1	1
40-49	34	16	10	4	4
50-59	28	13	12	1	2
60-69	11	7	3	1	0
70-79	17	8	5	2	2
Total	107	51 (47.7%)	37 (34.6%)	10 (9.3%)	9* (8.4%)

*Emergency cases for massive hemorrhage.

patient, and in the patient operated upon for chronic pyloric obstruction. This is a necessary safeguard to prevent regurgitation with resultant aspiration pneumonia and death.

Hemorrhage

Emergency Surgery

Recurrent bleeding and massive hemorrhage from a chronic duodenal ulcer continues to be a major indication and most serious problem in our group of patients. Massive hemorrhage, which occurs more frequently than any other type, poses the most challenging emergency situation of all complications arising from this disease.

Fifty-one (12%) of the entire series were operated upon as an emergency for massive bleeding. These patients had a history of active bleeding for a period of less than 24 hours on the average. This episode may have occurred prior to or during hospitalization. Generally, the period of surgical observation and therapy averages 4-6 hours in this group.

Postoperative Complications

The postoperative complication rate was higher in the emergency than in the elective groups.

Seventy-four complications occurred in 60 (9.8%) of the patients (Table 2).

Local Management of the Ulcer

Generally, the ulcer was managed in one of four ways, dependent upon the size and location of the ulcer, the condition of the patient and whether or not active bleeding was occurring from the ulcer site at the time of surgery. These policies were introduced in 1965 and have been used consistently since. Whenever it was best and safest, the ulcer was left in situ in the duodenum or on the head of the pancreas. In most cases, with active hemorrhage, the bleeding vessel in the ulcer bed was properly transfixed (multiple as required) and left in situ.

With the introduction of these new technical modalities, particularly with proper transfixation of the bleeding vessel, a greater number of the ulcers are now left in situ in the duodenum or freed from the duodenum and left on the head of the pancreas (Table 3).

Additional Procedures Performed

In 20% of the patients, additional procedures were performed at the time of the distal antrectomy-vagectomy. This factor can and does increase the surgical risks. The overall mortality (1.5%) is one per cent less in the distal antrectomy and vagectomy group.

Postoperative Gastric Analyses

Of the 476 patients tested repeatedly during a long followup period for free hydrochloric acid and total night resting secretory volume, the average was 260 cc (within normal limits). No free acid was present in 94.8% of the patients. This has persisted in repeated followup determinations. Only 5.2% (25 cases) showed free acids. In 9 of these, the free acids were within normal range being less than 20 mEq. In over 6, the free hydrochloric acid exceeded 20 mEq/12 hrs.

Marginal Ulcer

Only 4 (0.6%) patients of 597 who survived developed a marginal ulcer. These were due to incomplete vagectomies (vagotomies). These recurrences developed within 6-9 months following surgery.

Postoperative Gastrointestinal Roentgenographic Studies

Repeated postoperative followup gastrointestinal roentgenographic examinations conducted in 285 patients revealed a satisfactory functioning stoma with no prolonged delay in the emptying of the gastric remnant. The average emptying time of the stomach 6 months after operation was 75 minutes. After one year, the emptying time was normal with complete emptying in 30-40 minutes.

Repeated motor meal roentgenographic studies of the small bowel in 100 cases revealed clumping, segmentation, puddling, and motility disturbances in 40% of the patients. However, even though these changes were seen on roentgenograms, the patients had no sign or symptoms related to a disturbed function. By the end of the first year, a repeat examination of 100 patients revealed 90% to have a normal motor meal pattern and transit time.

Postoperative Deaths

Deaths occurring within 30 days of surgery from any

TABLE 4. *Causes of Death–611 Patients–14 Deaths.*

Age	Indication	Cause of Death	Non-Tech.	Tech.
55	Emergency	Pneumonia	x	
65	Emergency	Atelectasis	x	
70	Emergency	Pneumonia	x	
33*	Elective	Hepato-renal	x	
46†	Elective	Pancreatitis, acute		x
46†	Elective	Pancreatitis, necrotizing		x
51†	Elective	Pancreatitis (traumatic)		x
51*	Elective	Renal tubular necrosis	x	
65†	Elective	Pancreatitis, necrotizing		x
66	Elective	Pneumonia	x	
69	Elective	Pneumonia	x	
69	Elective	Pneumonia	x	
69	Elective	Myocardial infarction	x	
70	Elective	Toxemia, B. Welchii	x	

*Both patients extremely poor risks, both had recent massive hemorrhage from the ulcer site.

†These occurred in the early group of patients. Rarely occurs since ulcers are left in situ and a minimal degree of dissection about the head of pancreas.

cause are tabulated in Table 4. These include related, nonrelated and technical causes.

The overall mortality was 2.2%. In the 51 cases operated upon as an emergency for massive hemorrhage there were three (5.8%) deaths. In the elective cases the mortality was 1.4% and in this group of patients under 50 years of age, it was 0.6%. There were *no deaths* in 101 patients operated between 1968-1972 and in the first 114 consecutive patients during the first few years of this series.

The surgical risk was three times greater in the elective group of patients over 60 years of age. These deaths in many instances were not related to the surgical procedure per se.

In four (elective) patients death was due to acute pancreatitis, secondary to the resection of a penetrating ulcer. Most of these deaths can now be prevented by the method of technical management of the duodenal ulcer and in most instances by leaving the ulcer in situ. By adoption of this modality in the case of deep penetrating type ulcer, the mortality should be significantly reduced.

Three deaths in the elective group were unusual. A 67-year-old man died on the 3rd postoperative day from a fulminating staphylococcus pneumonia; a 70-year-old man died on the second postoperative day from a fulminating *Clostridium Welchii* infection (gas bacillus) of the abdominal and thoracic walls. This was the first infection of this type following gastric surgery for a duodenal ulcer seen by one of us (L.T.P.) in over 1,400 cases in 25 years. The third death was in a 51-year-old man on the 12th postoperative day from a renal tubular necrosis.

Evaluation of Followup Studies

Repeated followups were obtained in 542 patients for periods of one to 20 years; over 300 patients were followed for 10-20 years. This included also the necessary laboratory and x-ray studies.

Most of the patients were able to maintain themselves on 3 full meals per day with no moderate to severe dietary restrictions.

Sixty-two per cent maintained their weight whereas 21% gained weight. Only 3% lost weight because of surgery.

Moderate to severe dumping occurred infrequently after the first year. In none of the patients was it severe enough to warrant further surgery.

Diarrhea was troublesome and a recurring type in 3% of the patients. One patient was operated upon for intractable diarrhea. A reversed jejunal segment was interposed near the gastrojejunostomy with very good results (Table 5).

The overall evaluation of results in these patients, as estimated by the patient and examining physicians, was considered to be good to excellent in 86% to 91%, fair in 11% and 8%, and poor in 3% and 1%, respectively.

The ulcer recurrence rate was *only 0.6%* (four cases developed marginal ulcers in 6-9 months postoperatively).

Gallbladder Studies: Because of the reports that gallbladder stones are more frequent after truncal vagotomy, cholecystograms were obtained in 143 of our patients in all age groups at the 5-year followup examination. The incidence did not vary significantly with the same age group of the normal population without this type of surgery.

Comment

A number of important factors have come to the forefront as a result of this long range followup in our large series of cases.

The two major gastric secretory controls primarily concerned in the pathogenesis of a duodenal ulcer are adequately controlled, modified and/or eliminated by this surgical procedure. This fact is substantiated by the low incidence (0.6%) of marginal ulcer and by the absence of free hydrochloric acid in 95% of the cases. In addition, the total volume night resting secretory output is less than 260 cc. The success of this procedure, even though the entire antrum is not removed in all patients, is in consonance with the investigative laboratory physiologic findings of Moe and Harkins[7] that: 1) the antrum must be left in the acid stream; 2) it must be without stasis; and 3) it must be vagectomized. The motor meal emptying time in our studies attests to no delay in gastric reservoir emptying time.

Our data support two other important factors as related to the amount of gastric resection required and reservoir capacity function as related to postgastrectomy sequelae. A gastric resection greater than 25 per cent provides no additional protection against marginal or recurrent ulceration, but will create a higher incidence and increased severity of several of the postgastrectomy sequelae. The high incidence of recurrent and/or gastric ulcer or marginal ulcers following pyloroplasty with vagotomy or gastroenterostomy with vagotomy (5-12% reported) is usually due to delayed emptying of the stomach resulting in hyperfunction of the gastric antrum and/or incomplete vagus resection. This is true providing the gastric vagotomy is complete and there is no delay in the gastric emptying time.

The key to the whole problem of postgastrectomy and postvagotomy or vagectomy sequelae appears to be in the size of the gastric reservoir capacity which has normal emptying. This procedure provides for this by conservation of the entire gastric reservoir capacity which has no delay in emptying. This is accomplished with an antecolic Billroth II, Polya or Hofmeister type, anastomosis. A Billroth I gastroduodenostomy would result in delayed emptying and this would cause hyperfunction of any residual antrum. A Billroth I adds no distinct advantages to this procedure but instead may create many problems. However, it can be performed with some degree of safety in carefully selected patients.

Based upon our experience, there is no need to attempt to remove all of the proximal portion of the antrum. The limits of the antrum are variable and may occupy the distal 35% of the stomach.[2,3,8,12]

The significant reduction in the morbidity and mortality rates in those patients requiring emergency or urgent surgery for massive bleeding was based upon innumerable factors and not necessarily attributed to this procedure per se. The mortality was greatly influenced by the degree and duration of hemorrhage, the intercurrent diseases, the age of the patient (particularly so in patients over 60 years of age), the degree of liaison between the physician and surgeon, the effectiveness of organized positive treatment and ancillary supportive measures, surgical judgement and experience, election of the ideal time for surgical intervention, and the surgical procedure performed using seasoned judgement on the surgical technical management of the bleeding vessel. The latter is an important technical modality to be adapted to the existing local pathology in consonance with the surgeon's ability and experience. A continued decrease in both the morbidity and mortality rates can be expected by the application of these principles as experience is gained with time.

TABLE 5. *Results–542 Patients**

Weight	Per cent
Preop. maintained	62.4%
Gained	21.0%
Lost due to operation	3.1%
Lost—all causes	16.6%
Diet Restriction (moderate-severe)	0.4%
Dumping (moderate-severe)	0.4%
Diarrhea (moderate-severe)	3.1%
Ulcer, recurrence	0.6%

*No anemias or postop hiatal hernia.

With a policy of leaving the ulcer in situ whenever possible and particularly so in deep posterior penetrating ulcers on the head of the pancreas, the incidence of pancreatitis will be greatly diminished and the mortality from traumatic necrotizing pancreatitis will be practically eliminated.

One of the objections raised by a number of surgeons concerning this procedure is leakage and mortality associated with the risk involved in duodenal stump closure. As noted in this series, there were no deaths from duodenal leakage or perforation. Also, the incidence of this complication was about one per cent. By the application of careful technique in respect to this aspect of the procedure, avoidance of this complication is possible. Early clinical recognition of this complication postoperatively can be the key to preventing death by early drainage of the stump area. Drainage of this area is not provided at the time of surgery except in the rare and occasional case. It was employed about once in every 150 cases. In these few instances of a difficult mobilization problem and insecure closure of the stump, the surgeon provided for drainage at the time of the distal antrectomy.

The elderly patient is always an increased surgical risk because of his physiologic age processes. Superimposed upon this usually are a number of intercurrent diseases or conditions, any of which can be life threatening under the stress of surgery and/or hemorrhage. It should be noted that 66% of the deaths (3%) in this series were in patients over 65 years of age. The patients in this age group represented only 16% of the entire series. The increase in the mortality rate in recent years in our group has been due to this factor of age in poor risk patients and not necessarily due to the procedure per se. We use other conservative surgical procedures to meet the exigency of the situation as related to local pathologic and systemic problems. For example, transfixation of the bleeding point combined with our procedure or a pyloroplasty; in a poor risk elderly patient with prolonged obstruction and chemical imbalance, a gastroenterostomy with or without a vagectomy is accomplished. By the application of these basic principles in the elderly poor risk patients, some improvement in the morbidity and mortality rates can be expected.

Since the surgical risk is much greater in this group of elderly patients, it is important that surgical intervention, when indicated, be carried out before the patient becomes too old. Frequently these patients have had a history of duodenal ulcer and associated complications for 10-20 years. If complications of chronic duodenal ulcer occur, our medical colleagues can do a real service to the patient and to us as surgeons in referring these patients for consultation earlier. Under these more favorable circumstances, the new and conservative surgical procedures can be performed with a mortality of 0.5 to one per cent.

During the past several years, distal antrectomy-vagectomy was performed in 70% of the patients operated upon for duodenal ulcer, whereas in the remaining 30% three other conservative surgical procedures were employed: pyloroplasty-vagotomy, gastroenterostomy and occasionally hemigastrectomy-vagotomy.

The surgeon today has these to select from and can pattern the procedure to meet specific and individual problems.

We keep an open mind with a watchful eye on the newer highly selective denervated gastric procedures. If and when these reach beyond the goals already obtained by these new procedures, we will adopt these in specially selected patients.

We can say for certain that the past 32 years have been the greatest era in the Evolution and Revolution in Surgery for Duodenal Ulcer. The future holds interesting challenges and finally the discovery of the true nature of this disease.

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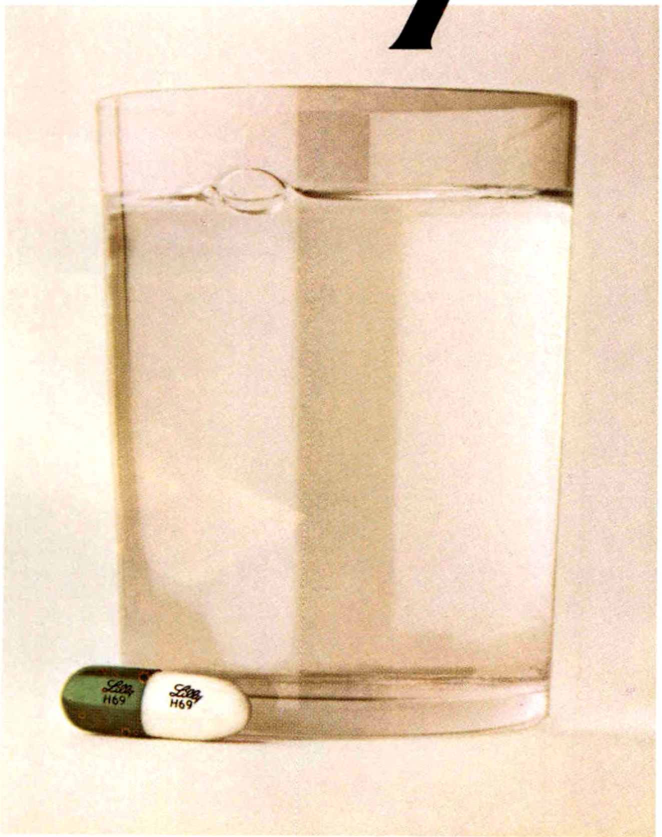

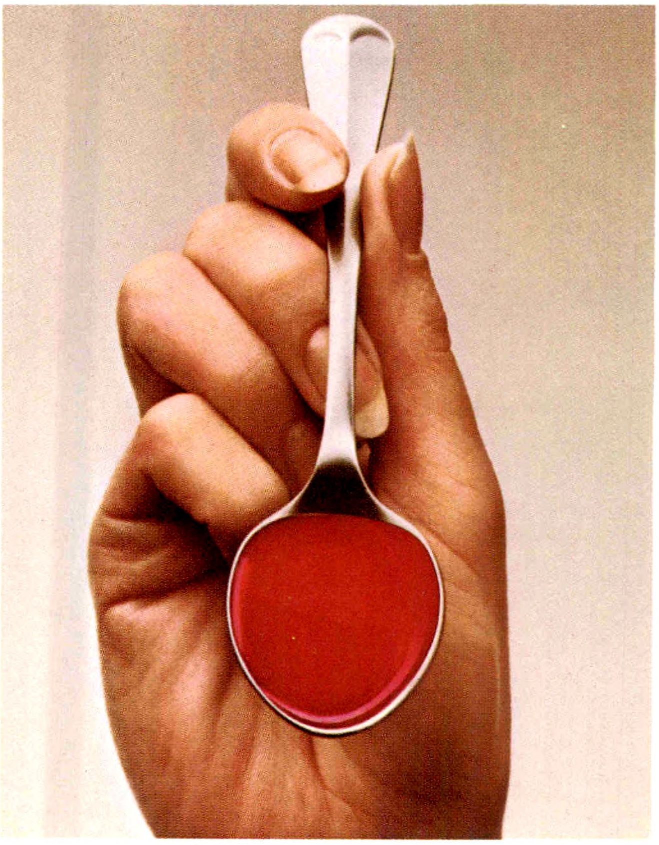

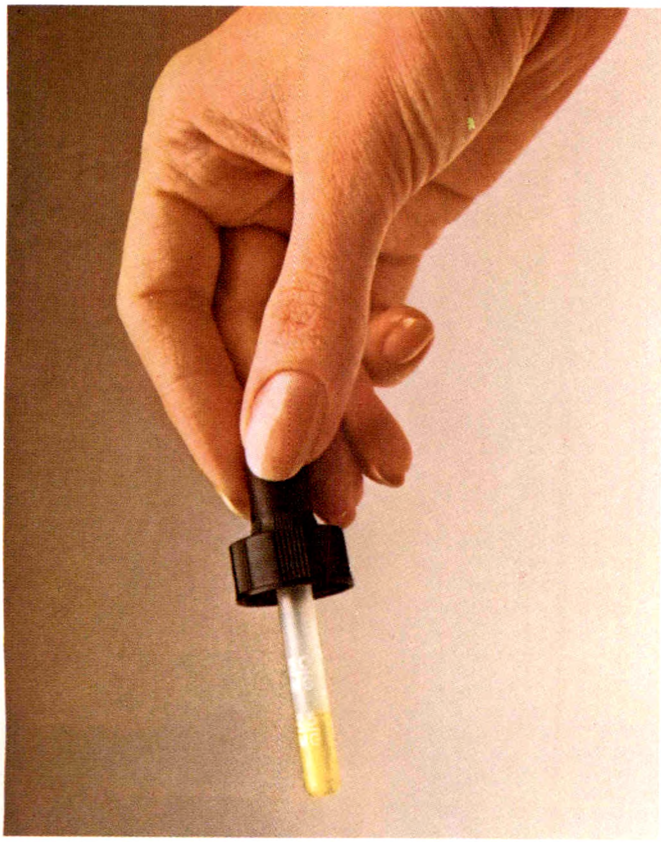

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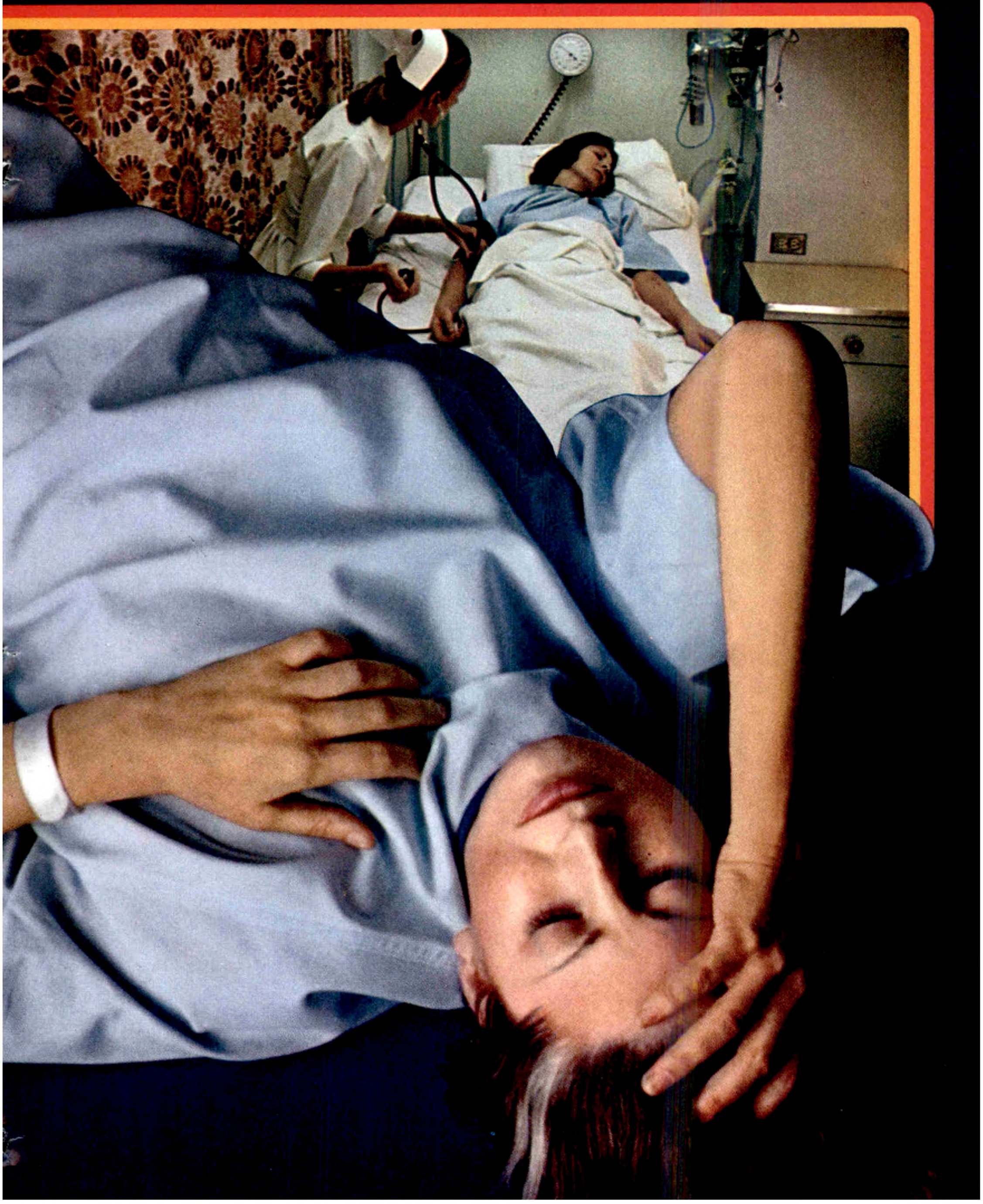

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Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see Indications section).

Each gram (10 ml of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium.

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group, and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every six hours for eight doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/ml one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/ml after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/ml over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/ml in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

In accord with the concepts in the Warning Box and this Indications section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.

1. Acute infections caused by *S typhi**

   It is not recommended for the routine treatment of the typhoid carrier state.
2. Serious infections caused by susceptible strains in accordance with the concepts expressed above.
   - a) *Salmonella* species
   - b) *H influenzae,* specifically meningeal infections
   - c) Rickettsia
   - d) Lymphogranuloma-psittacosis group
   - e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   - f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents
3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS

1. Base line blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.
2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.
4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.
5. There are no studies to establish the safety of this drug in pregnancy.
6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).
7. Precaution should be used in therapy of premature and full-term infants to avoid gray syndrome toxicity. (See Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the newborn infant.
8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes, and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding (1) the size of the population at risk, (2) the total number of drug-associated dyscrasias, and (3) the total number of nondrug-associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases, therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after three to four days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
  - (1) abdominal distension with or without emesis;
  - (2) progressive pallid cyanosis;
  - (3) vasomotor collapse, frequently accompanied by irregular respiration;
  - (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/ml) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 ml of an aqueous diluent such as water for injection or 5% dextrose injection.

DOSAGE

Adults

Adults should receive 50 mg/kg/day in divided doses at six-hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg/kg/day divided into four doses at six-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled Gray Syndrome under Adverse Reactions.)

A total of 25 mg/kg/day in four equal doses at six-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into four doses at six-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

HOW SUPPLIED

NDC 0071-1089-10 (Steri-Vial® No. 57)

Chloromycetin (chloramphenicol) Sodium Succinate is supplied as a dried powder in Steri-Vials (rubber-diaphragm-capped vials). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per milliliter (1 g/10 ml). Available in packages of 10 vials.

CHLOROMYCETIN, brand of chloramphenicol. Reg US Pat Off RJ

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PARKE, DAVIS & COMPANY, Detroit, Michigan 48232

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*In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

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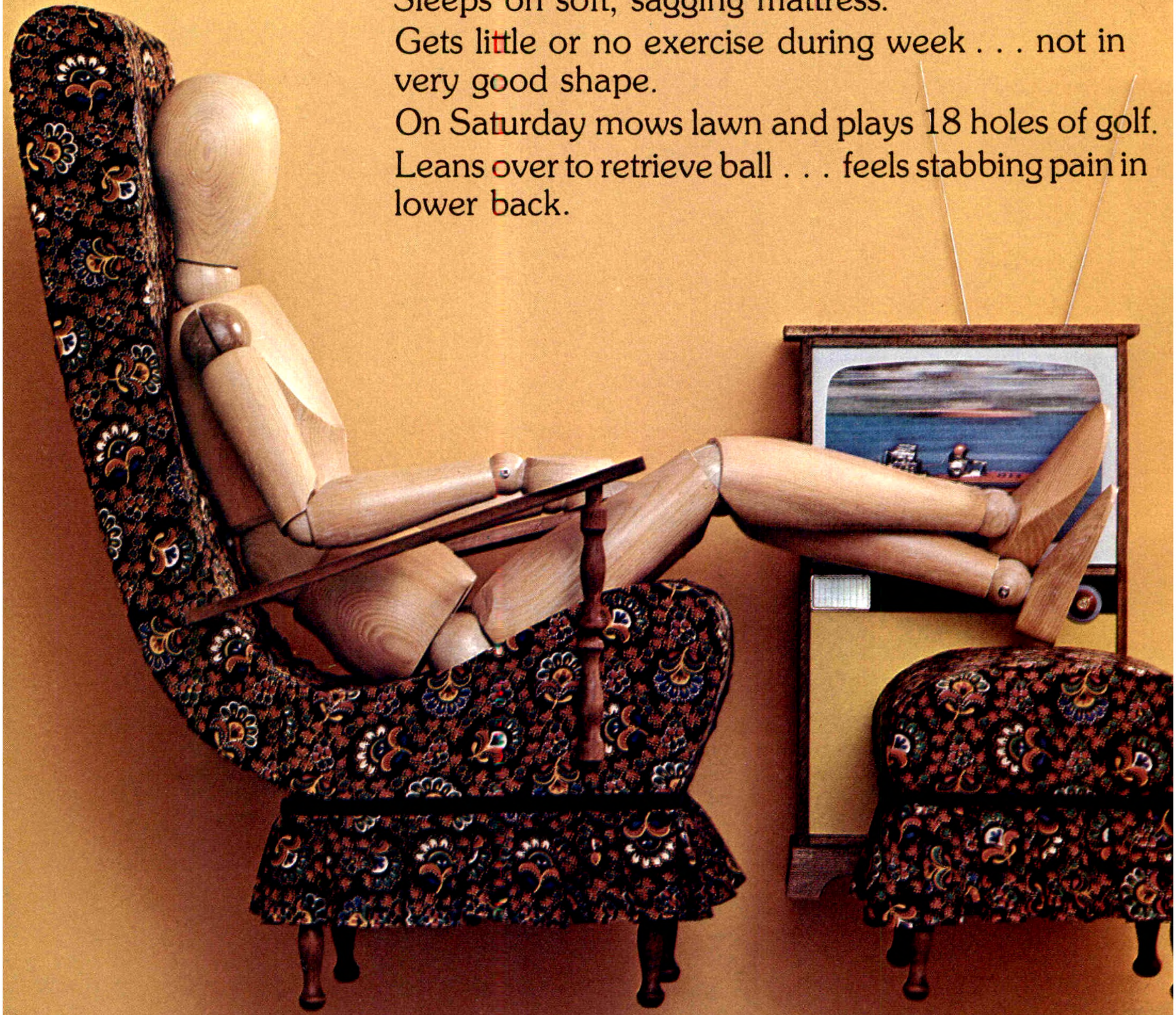
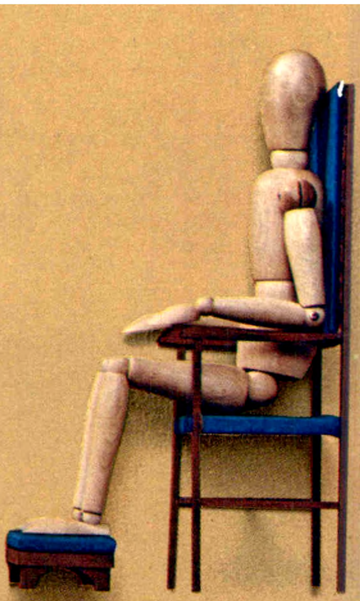
Gets little or no exercise during week . . . not in very good shape.
On Saturday mows lawn and plays 18 holes of golf.
Leans over to retrieve ball . . . feels stabbing pain in lower back.



the solution:



At work sit in straight chair with firm back . . . knees higher than hips. Prop feet on small footstool to elevate knees. Don't sit in overstuffed furniture. Never sit long in one position . . . get up frequently and move around. Exercise regularly to strengthen abdominal and low-back muscles and help prevent weekend flare-ups. Avoid sudden spurts of vigorous physical activity. A back support can help relieve pain and fatigue.

to relieve discomforts associated with acute, painful musculoskeletal disorders...

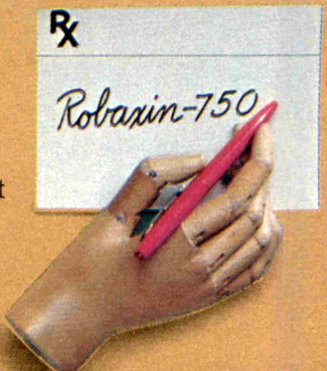
ROBAXIN®-750

brand of **methocarbamol** 750 mg. capsule-shaped tablets

the Robaxin Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood ½-¾″ thick between mattress and box springs. The use of moist heat is often very beneficial.

Robaxin-750 is often indicated to relieve the discomforts associated with acute, painful musculoskeletal disorders. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.



Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.

Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:
ROBAXIN® (methocarbamol) 500 mg.

See package insert for full prescribing information.

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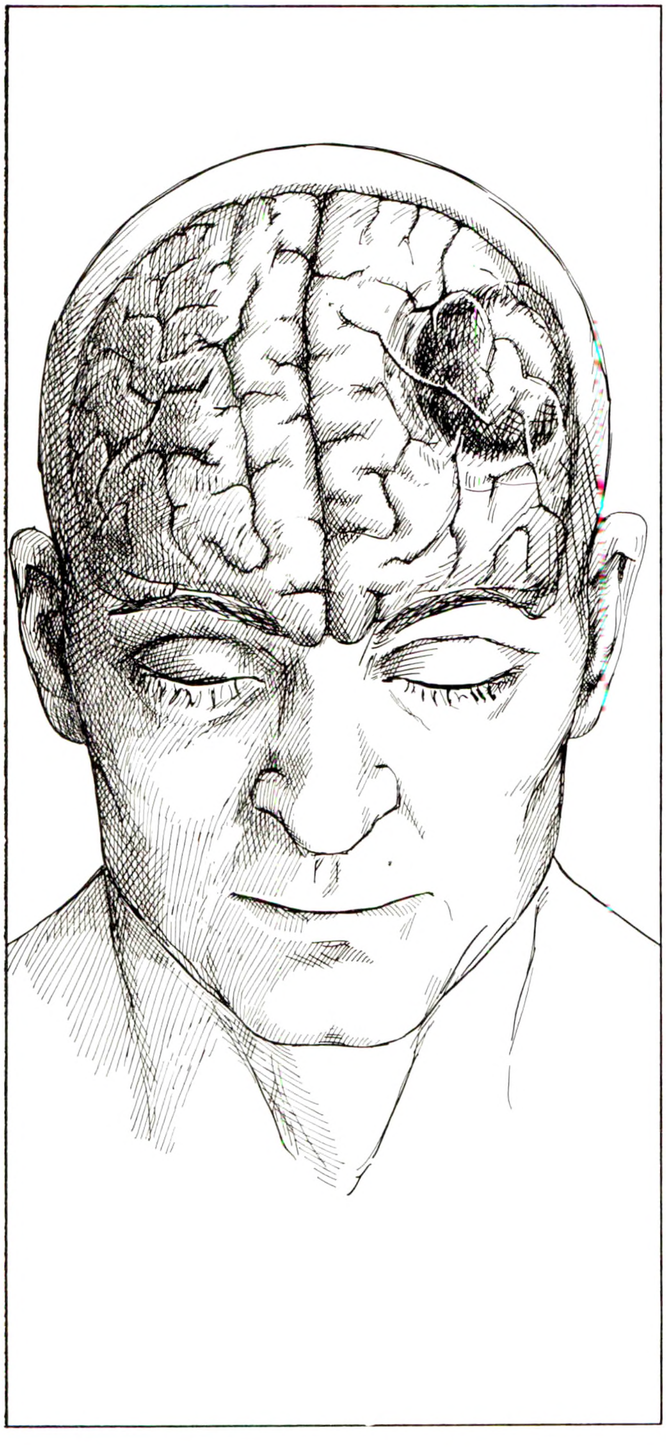
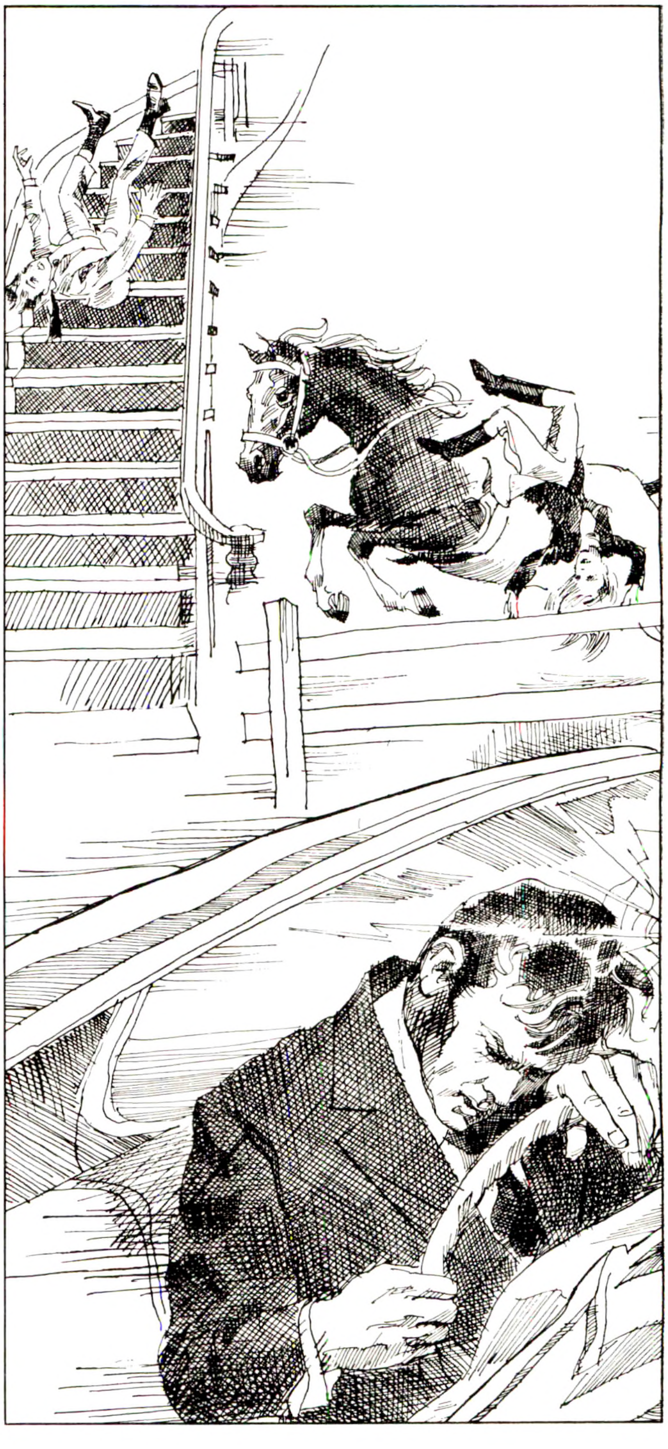
cerebral

expect it as a possible complication of primary or metastatic brain tumor.

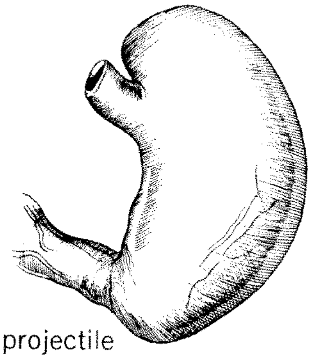


expect it in the presence of severe head injury.

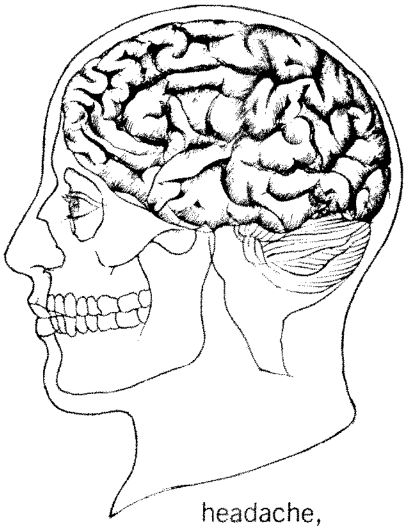


edema*

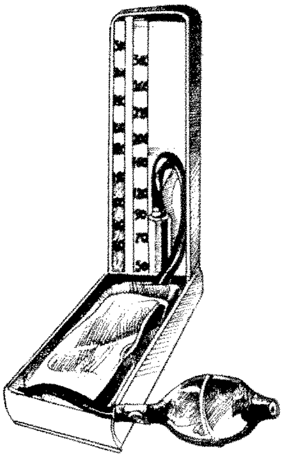
suspect it in the presence of signs and symptoms such as these:



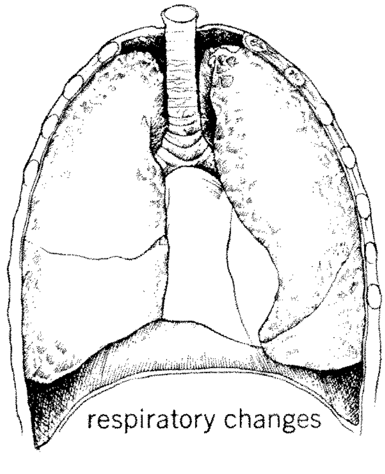
projectile
vomiting



headache,
altered consciousness

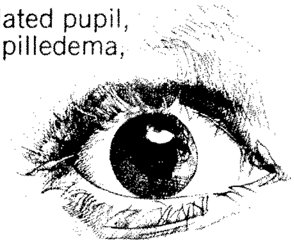


increased
blood
pressure

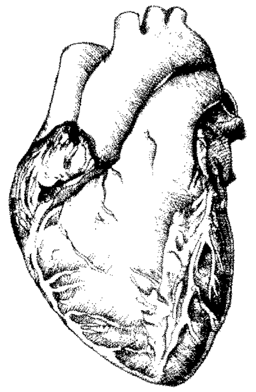


respiratory changes

dilated pupil,
papilledema,



unilateral or bilateral
abducens palsy



bradycardia

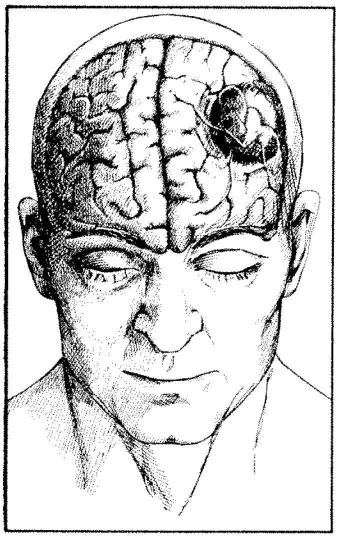
***Note: The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.**

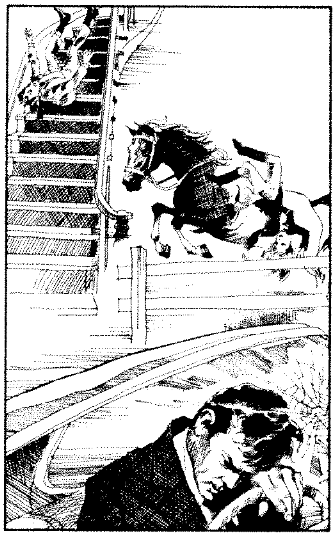
Injection:
4 mg/ml Phosphate

Tablets:
4 mg, 1.5 mg, 0.75 mg, 0.5 mg, 0.25 mg

an indication for **DECADRON**® (Dexamethasone Sodium Phosphate|MSD) and **DECADRON**® (Dexamethasone|MSD)

For a brief summary of prescribing information, please see following page





Injection Decadron® Phosphate

(Dexamethasone Sodium Phosphate|MSD)

"Some degree of edema accompanies most head injuries. Various methods have been used to control this, but at present the most efficient method is use of... dexamethasone [DECADRON®]... .The effect of this is not well understood, but there is little question that edema of the brain is significantly lessened by its use."

Ritchie WP: The emergency care of cerebral injuries, J Lancet *86*:255, June 1966.

The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

Dosage for cerebral edema

Injection DECADRON Phosphate is generally administered initially in a dosage of 10 mg dexamethasone phosphate (2.5 ml) IV followed by 4 mg dexamethasone phosphate (1 ml) IM every six hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For the palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy should be individualized with either Injection DECADRON Phosphate or Tablets DECADRON (supplied as 4.0-, 1.5-, 0.75-, 0.5-, and 0.25-mg tablets). Two mg two or three times daily may be effective. The smallest dosage necessary to control cerebral edema should be utilized. The usual precautions in regard to corticosteroid therapy should be employed, and antacids, anticholinergic drugs, and diet measures to prevent gastrointestinal ulcer or hemorrhage should be considered. Please read the brief summary below, and consult full prescribing information before prescribing or administering.

Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction; hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

How Supplied: Tablets in five strengths: 4 mg dexamethasone, in bottles of 50 and single-unit packages of 100; 1.5 mg dexamethasone, in bottles of 50; 0.75 mg dexamethasone, in 5-12 PAK® (package of 12), single-unit packages of 100, and bottles of 100 and 1000; 0.5 mg dexamethasone, in bottles of 100 and 1000; and 0.25 mg, in bottles of 100. Injection, in 1-ml disposable syringes and 1-ml, 5-ml, and 25-ml vials, containing per ml: dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone, 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, water for injection q.s. 1 ml, and 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

Tablets
DECADRON®
(Dexamethasone|MSD)

Injection Phosphate
DECADRON®
(Dexamethasone Sodium
Phosphate|MSD)

MSD
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See next page for summary of prescribing information.

On the surgical service…

Clinical confidence earned through experience

Keflin® I.V.

sodium cephalothin

2 Gm.* in 100-ml. ampoule

The confidence that comes with 10 years' experience†

Experience with Keflin has established a record of clinical effectiveness in serious skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella.*

*Equivalent to cephalothin.

†Keflin became available for clinical investigation early in 1962 and to the profession in 1964.

Brief Summary. Consult the package literature for prescribing information.

Indications: Keflin® (sodium cephalothin, Lilly) is indicated for the treatment of serious infections caused by susceptible strains of the designated micro-organisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella*

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [020774S]

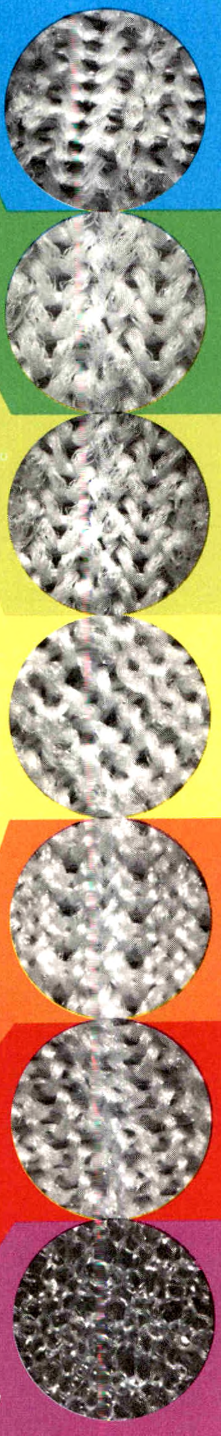
Lilly

400402

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

Because tubular design provides proper graduated compressi



The knit is looser at the proximal end of the Zimmer anti-embolism stocking to accommodate the large circumference of the thigh without tourniquet effect. A unique thin foam lining and insert* helps keep the stocking up even when the patient is ambulatory.

The open knit above the knee exerts minimal compression so it will not inhibit blood flow being forced through the venous system by tighter compression distally on the leg.

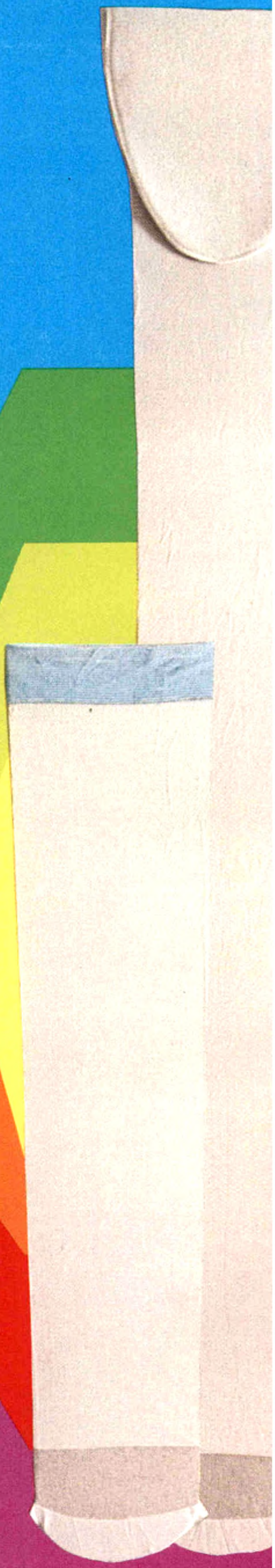
The knit loosens significantly at the knee to minimize pressure on the popliteal vein.

The tight knit over the calf forces the blood into the deep system while it compresses the superficial veins.

The knit is tightest at the ankle to provide the greatest compression distally.

A wide band of lighter knit material facilitates easy application of the stocking and proper fit around the heel and instep.

The transparent toe window allows a quick check of blood circulation without removing or adjusting any portion of the stocking.



* Patents Applied For

the new Zimmer anti-embolism stocking

PATENTS APPLIED FOR

Correct graduated compression is now controlled by a single variable — the tightness of the stitch at a given circumference.

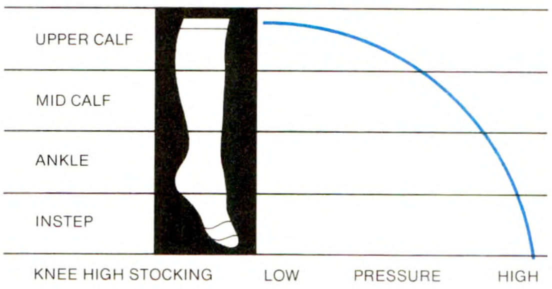
The new tubular design anti-embolism stocking from Zimmer•USA precisely controls compression through the amount of elasticity knitted into the stocking. This unique variable knit* is precisely controlled during manufacture with sophisticated, programmable knitting machines. Because precise control is exercised over the knit at any circumferencial point on the leg, the Zimmer anti-embolism stocking provides gradually decreasing pressure that enhances the venous return mechanism. Tightness of the knit is the key factor controlling the amount of compression.

*Patents Applied For

It shapes itself to fit virtually any leg.

Because no two legs are exactly alike, any pre-shaped anti-embolism stocking may not exactly match the contours of an individual patient's legs. Improper fit could cause constriction at some point on the leg. The stocking's tubular design adapts itself to even slight variations in the contour of a patient's legs and provides correct graduated compression through its built-in graduated elasticity. Available in many size and style combinations — 36 in all — to assure a correct fit for virtually any patient.

GRADUATED COMPRESSION CURVE



CLINICAL REFERENCES available on request from Zimmer•USA

CONTRAINDICATIONS: Do not use in the presence of potentially compromised vascular circulation, i.e.: arteriosclerosis, congestive failure, massive edema, etc. Not recommended for use in the presence of open skin lesions or disease. Do not use over the thigh when the thigh circumference is greater than 28".

WARNING: Use proper size of stocking for the patient. Be sure heel is placed in the heel instep band. Discontinue use if circulation is compromised as indicated by pain, loss of capillary pulse in toes, etc. Do not roll down the top of stocking as a tourniquet effect may occur. CAUTION: Federal law restricts this device to sale by or use on the order of a physician.

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COMPLICATIONS IN VASCULAR SURGERY

Edited by Hugh G. Beebe, M.D. With 18 Contributors.

Outstanding vascular surgeons from all sections of the country have pooled their composite experience and knowledge for this in-depth work. Each has written on a specific vascular complication and gives you the benefit of his expertise in this area. Three objectives are always in view: 1) To help you prevent complications where the causes are known and can be anticipated. 2) To provide you with a clear guide to the management of complications. 3) To establish a foundation of information from which you can deal logically and effectively with problems not described.

This work reaps the benefit of significant appraisals of the long-term follow-up studies that became possible during the last ten years. An analysis of the results obtained with various surgical approaches during that time has made it now possible and practical to develop meaningful guidelines.

The surgeon can refer to this authoritative, practical atlas-text with confidence.

402 Pages • 175 Illustrations • 1973 • $28.00

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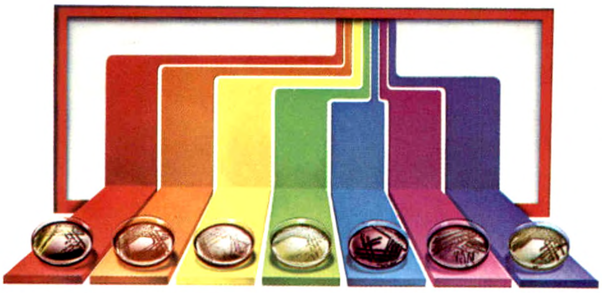
Schering

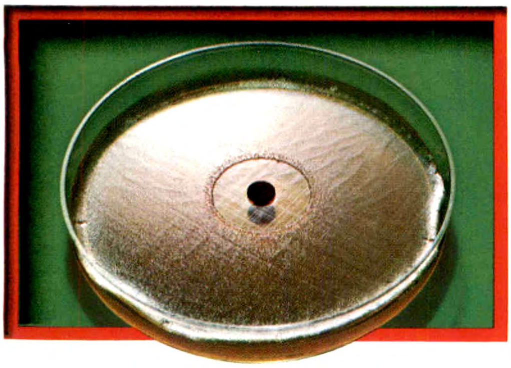
In serious gram-negative infections*

Three good reasons to initiate therapy with Garamycin® Injectable

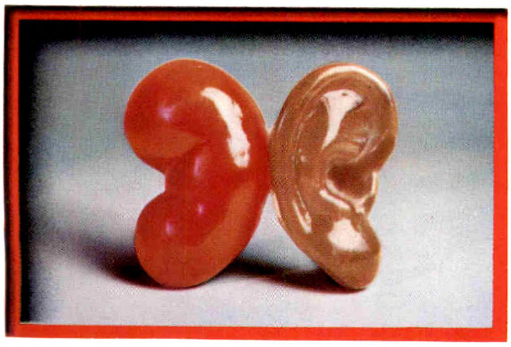
(gentamicin sulfate)



1. Unique spectrum.



2. Incidence of bacterial resistance is low and has not increased significantly.



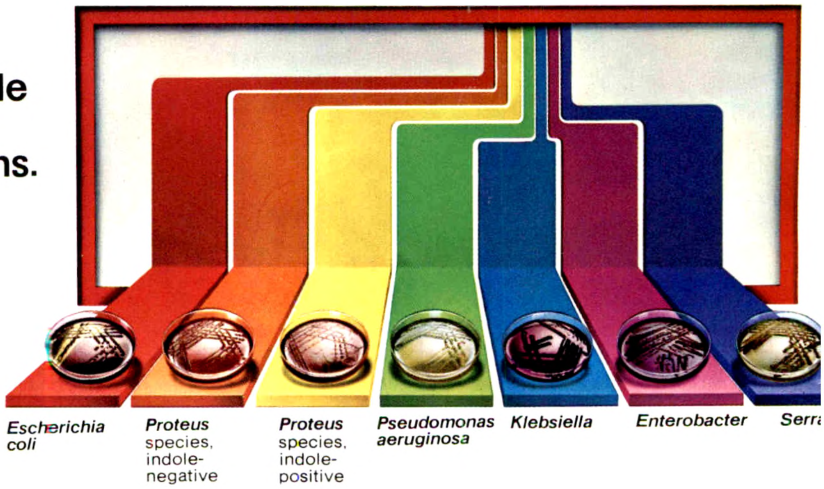
3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

*Due to susceptible organisms

1. Unique spectrum.

Garamycin Injectable (gentamicin sulfate) is active against susceptible strains of seven major gram-negative pathogens.
These are:

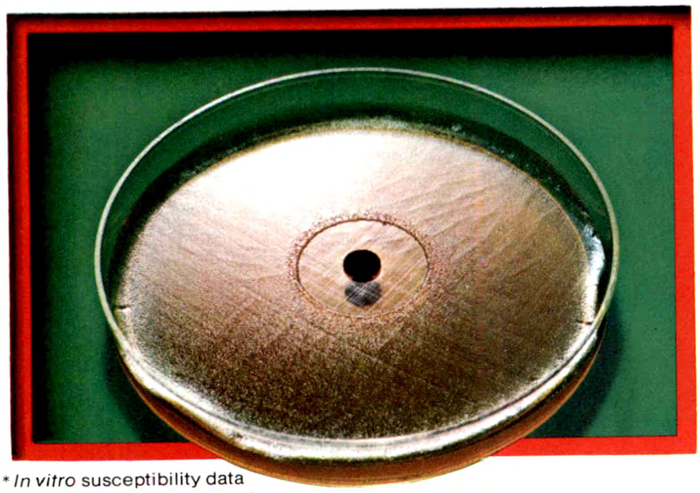
Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella } species
Enterobacter } species
Serratia } species


Escherichia coli
Proteus species, indole-negative
Proteus species, indole-positive
Pseudomonas aeruginosa
Klebsiella
Enterobacter
Serr

Garamycin Injectable is also highly effective against susceptible strains of **Staphylococcus aureus** and may be considered when penicillins are contraindicated.

2. Incidence of bacterial resistance is low and has not increased significantl

*In vitro** susceptibility virtually unchanged



* *In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.

In a five-year study[1] in over 100 hospitals, gram-negative pathogens identified and tested demonstrated high susceptibility to GARAMYCIN. From 1970 through 1974, there was virtually no change in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

In the seven or eight years' experience of one investigator[2] where gentamicin has been restricted to parenteral use, resistance has not appreciably changed.

Resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported.

References

1. I.M.S. Audit of Pathology Cultures—1970-74.
2. Jackson, G.G.: Highlights of a Symposium on Gentamicin, a filmed panel discussion summarizing a symposium on gentamicin, University of California School of Medicine, Los Angeles, January 26, 1971.

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Schering

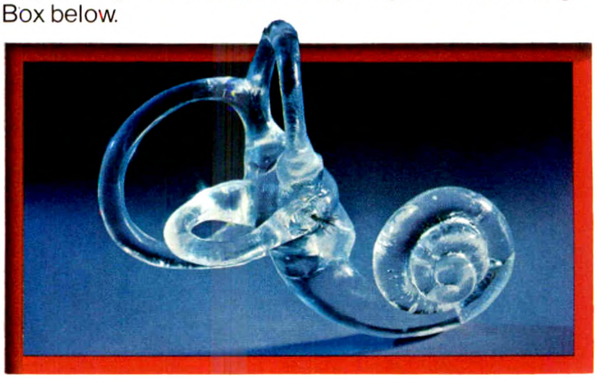
3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

Adverse renal reactions

The risk of adverse renal reactions is low in patients with normal renal function. Usually manifested by nitrogen retention as evidenced by a rising BUN and creatinine, they occur most often in patients with pre-existing renal damage and in patients receiving larger than recommended doses or treated for longer periods of time than recommended. See Warning Box below.

Adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions with GARAMYCIN Injectable is relatively low. When occurring, the effect is predominantly on the vestibular branch of the eighth cranial nerve, resulting in vestibular dysfunction with vertigo and tinnitus. These symptoms have, in many cases, been transitory. The known effect on the auditory branch to date mostly has involved only the high-frequency hearing ranges. See Warning Box below.



A logical choice

in serious gram-negative infections†

- **pneumonia**
- **urinary tract infections**
- **septicemia**
- **wound infections**

† Due to susceptible organisms

Garamycin®
gentamicin sulfate
injectable
40 mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

See Clinical Considerations section which follows...

A logical choice
in serious gram-negative infections*

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin
For Parenteral Administration

> **WARNING**
> **Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.**
>
> **Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.**
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>
> **The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.**
> **USAGE IN PREGNANCY Safety for use in pregnancy has not been established.**

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura, fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal functio is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg (1.5 ml.) three times daily.

In patients with life-threatening infection dosages up to 5 mg./kg./day may be administered in three or four equal doses. T dosage should be reduced to 3 mg./kg./da as soon as clinically indicated.

**In children and infants, the newborn, an patients with impaired renal function, dosag must be adjusted in accordance with instru tions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscul route is not feasible (e.g., patients in shock, with hematologic disorders, with severe bu or with reduced muscle mass).

For intravenous administration, in adults, single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile norma saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The conce tration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused o a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recomme for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) 2 ml. (80 mg.) disposable syringes for pare teral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

010 JULY
AHFS Category 8:1

For more complete prescribing details, consult Package Insert or Physicians' Des Reference. Schering literature is also available from your Schering Representati or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Garamycin®
gentamicin sulfate
injectable
40 mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

*Due to susceptible organisms

The Incidence and Management of Pulmonary Mycosis in Renal Allograft Patients

STEPHEN A. MILLS, M.D.,* H. F. SEIGLER, M.D.†
WALTER G. WOLFE, M.D.†

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710

A retrospective analysis of 193 renal transplant recipients yielded 15 patients who developed pulmonary mycosis post-transplantation and one case in which mycotic lung infection existed at the time of transplant surgery. Agents responsible for infection included *Nocardia asteroides* in 8 cases, *Aspergillus flavus* in 5 cases, *Cryptococcus neoformans* in 4 patients and *Candida albicans* in 2 cases. Two cases had mixed mycotic infections. Ten patients died, of which 7 had diagnosis established antemortem. Two cases had diagnosis established by thoracotomy and 1 case by transtracheal aspiration. Problems in establishing accurate diagnosis are discussed with emphasis placed on the need for more frequent use of transtracheal aspiration and thoracotomy for precise diagnosis.

SEVERAL AUTHORS have documented a high incidence of fungal and nocardia infections complicating renal transplantation.[10,11,14,16,17] The earlier introduction of adrenal corticosteroids,[23] antibiotics[23,28] and cytotoxic drugs[6,12] has also been followed by a rise in mycotic infections.

Infection in renal transplant patients often follows rejection episodes and their treatment.[2] Diagnosis of mycotic infections in these patients is often made only at autopsy or terminally when therapy has been ineffective.

The purpose of this report is to describe experience with 16 pulmonary mycotic or nocardia infections following renal transplantation. There are 6 survivors. Of 10 deaths, 7 had diagnosis established antemortem.

Methods

A retrospective analysis of 193 patients undergoing renal transplantation at Duke and the Durham Veterans' Administration Hospital from February 26, 1965 through August 26, 1973, yielded 16 patients with pulmonary nocardia or mycotic infection. Criteria for selection included isolation of nocardia or fungus from pulmonary secretions or histological demonstration of fungus with or without cultural identification. Culture and antibiotic sensitivity determinations were performed using standard techniques.

Postoperative immunosuppression was similar in most cases and consisted of Azathioprine 100 mg/day beginning the day prior to transplantation, and Prednisone 20-60 mg/day in divided doses. Two patients received ALG. Episodes of threatened rejection were treated with intravenous Methylprednisone 1 gr/day, oral Prednisone 200 mg/day and local irradiation to the graft, 900 RADs over 5 days.

All patients were under the care of the Nephrology Staff in hospital clinics.

Results

Sixteen of 193 renal transplant patients developed pulmonary nocardia or fungal infections, an incidence of 8.3%.

Eight of 16 infections were in patients receiving cadaveric renal transplants, an incidence of 50%. There were 90 cadaveric transplanted kidneys in the series of 193 patients, an incidence of 47%. The remaining 8 pulmonary fungus infections occurred in patients with living related non-HL-A identical donor kidneys, an incidence of 50%. Living related, non-HL-A identical donors comprised 36.2% or 70 of the transplants performed in this period. None of the patients in the infected group had an HL-A identical donor, while 17% of the 193 renal transplants had an HL-A identical donor.

Submitted for Publication March 19, 1975.

Supported in part by Clinical Research Center Grant No. CA 11265 and Grant No. 5 PO1 Am13084-11, from the National Institute of Health.

*Research Fellow.

†Associate Professor.

TABLE 1.

Case	Age (yrs) & Sex	Primary Disease	Donor	Diabetic	Number of Rejection Episodes	Onset infect. Month post TP	Organism	Non Pulmonary Sites
1RH	34M	C-G-N	LRD* (2nd) Transplant	No	2	3	Nocardia	——
2JD	42M	Malignant Hypertension	LRD	No	1	27	Nocardia	——
3VD	21M	C-G-N	LRD	No	0	6	Nocardia	Brain
4JG	47M		Cad†	Yes	0	5	Nocardia Rhinosporosis	
5LW	20M	Nephrotic Syndrome 2° A-G-N	LRD 2nd plant	No	0	7	Nocardia	Brain
6JN	33M	C-G-N	LRD	Yes	1	2	Nocardia Aspergillus	—— ——
7WC	49M	Malignant Hypertension	Cad	Yes	0	3	Aspergillus	——
8CB	46M	Systemic Beryllosis	Cad	No	0	4	Aspergillus	GI
9PED	23M	C-G-N	LRD	No	2	4	Aspergillus	
10FH	43M	Malignant Hypertension	Cad	No	2	1	Aspergillus Nocardia	——
11GB	56M	C-G-N	Cad 2nd plant	No	0	5	Cryptococcus Nocardia	Brain
12ED	30M	C-G-N	LRD	No	0	0	Cryptococcus	Brain
13TC	49M	C-G-N	Cad	No	0	61	Cryptococcus Chromomycosis	Brain Skin
14CG	35M	C-G-N	Cad	No	0	37	Cryptococcus	——
15GP	33M	WRM-H	LRD	No	3	0	Candida	——
16WP	26M	C-G-N	Cad	No	1	7	Candida	——

*Living Related Donor
†Cadaver

All patients in the infected group were male while in the entire series 70.4% of the patients were male.

Four deaths were from the group with living related donor transplants and 6 deaths occurred in the group of 8 infected patients with cadaveric transplants.

Table 1 summarizes pertinent clinical data as to type of infecting organism, number of rejection episodes, time of onset of the pulmonary infection after renal transplantation, symptoms, extrapulmonary sites of fungal infection, admission chest x-ray and laboratory data. Results are further analyzed according to type of fungal organism isolated. Table 2 summarizes the mode of diagnosis, treatment and outcome.

Nocardosis

Eight patients had nocardial pulmonary infections. Three of these had associated pulmonary mycoses, 1 having associated pulmonary aspergillus, 1 with pulmonary cryptococcosis and meningitis, and the third having pulmonary rhinosporosis. Five patients lived and 3 patients died.

Onset of the nocardial infections ranged from 1 to 27 months after transplantation. Seven patients gave a 1 to 7 day history of fever, cough, pleuritic chest pain and myalgia. The eighth patient was semi-comatose on a mission. One patient developed mild transient rig hemiparesis associated with abnormal brain sca another had multiple nocardial brain abscesses der onstrated at autopsy.

Case Reports

Chest x-ray revealed pulmonary infiltrates in 7 pateints and cavitati in one. Pleural effusions were present in 2 cases. Pulmonary infiltrat progressed to cavitation in 5 cases.

Sputum gram stain or culture yielded the diagnosis in 5 cases, tran tracheal aspiration in 1 and open lung biopsy in 1 case.

Case 2 had numerous bacterial pathogens demonstrated on repeat sputum specimens with nocardia being demonstrated only once. Ho ever, repeated transtracheal specimens consistantly yielded *Nocard asteroides* and resulted in institution of triple sulfonamide and Ampic lin therapy with a favorable outcome. Prednisone was tapered from mg/day to 20 mg/day and Imuran from 100 mg/day to 25 mg/day follo ing diagnosis.

Case 3 (Fig. 1) had multiple sputum cultures showing other bacter pathogens and obscuring correct diagnosis. Prednisone was reduc from 60 mg/day to 35 mg alternate days and Imuran reduced from 1 mg/day to 25 mg/day. Diagnosis and treatment of nocardiosis was ma only after one week of hospitalization and did not prevent death fro disseminated nocardiosis despite Gantrisin therapy. Early lung biop may have been valuable in this case.

Case 4 developed cough and pleuritic right chest pain while hc pitalized for treatment of a bacterial pyarthrosis of the right hand. Che

TABLE 1. *(continued)*.

		At Infection Onset					
Symptoms	Chest X-Ray	WBC	Prednisone	Imuran	BUN	CR	Creatinine Clearance ml/min
4d cough, chest pain, fever	RLL infiltrate R pleural effusion	6,700	40	25	63	6.3	—
3d chest pain, malaise	RUL infiltrate R&L pleural effusions	9,200	60	100	36	1.9	43
4d fever, cough, yellow sputum	LLL infiltrate	9,500	60	100	25	1.8	37
1d fever, semicomatose	RUL cavity	25,800	40	75	28	0.8	71
3d fever, cough, headache	R lung abscess	10,000	75	30	22	1.1	43
7d cough, fever, R chest pain	RLL infiltrate	9,300	860	100	18	1.3	80
30d fever, cough, yellow sputum	LUL infiltrate	9,800	45	50/75	53	1.2	—
hemoptysis x 14 months 3 wk. fever, cough	LL bilateral infiltrates	7,800	25	50	20	0.7	—
1d cough, pleuritic chest pain	bilateral infiltrates	16,000	80	100	130	2.6	42
fever, cough, chest pain	L hilar cavitation RLL abscess	13,000	40	75	44	2.5	—
1 wk. fever, headache, blurred vision	RLL infiltrate LLL cavitation	16,700	100	75	41	1.5	46
lassitude	bil. infiltrates	7,200	120	100	31	1.2	67
cough, yellow sputum, headache, nausea vomiting	RUL infiltrate & nodule	10,100	20	100	26	0.5	—
—	LLL mass	8,900	25	100	11	1	—
—	RLL cavitation	12,500	—	—	—	—	—
—	RLL infiltrate	500	45	100	53	2.2	20

x-ray revealed a right upper lobe infiltrate, right pleural effusion and some haziness in the left lower lung field. Multiple cultures of sputum, CSF, urine, blood and pleural fluid were negative. The hand infection resolved uneventfully after drainage cultured *E. coli* and klebsiella; Keflin and Kanamycin were administered. Serial chest x-rays revealed clearing of the right pleural effusion with cavitation of the right upper lobe infiltrate (Fig. 2). Prednisone was maintained at 40 mg/day and Cyclophosphamide 50 mg/day was substituted for Imuran due to concern over the possibility of Imuran hepatotoxicity. Five months after this hospitalization and 10 months after renal transplantation, the patient was found to be febrile and semi-comatose at home. Neurological examination revealed no localizing or lateralizing signs. The patient responded only to noxious stimuli. WBC was 28,500, hemoglobin 13.2 gr%, BUN 23; arterial blood gases showed a P_{O_2} of 75, P_{CO_2} of 16 and a pH of 7.57. EKG showed no significant changes. Chest x-ray showed the previously described right upper lobe lung abscess. Lumbar puncture was normal. With the impression that the patient had septicemia, he was treated with fluids, antibiotics and high dose steroids. However, he pursued a rapid downhill course and died 12 hours after admission. Autopsy revealed massive nocardia bronchopneumonia and a 3 x 3 cm abscess in the right lung containing nocardia and rhinosporosis. The abscess extended into the main pulmonary artery.

Comment: Persistent undiagnosed pulmonary cavitation 5 months after renal transplantation progressed to massive nocardial bronchopneumonia and death at 10 months. Surgical diagnosis was required here at an early stage.

Case 5 received a cadaveric renal transplant at the age of 18, but rejection required transplant nephrectomy 2 months later. Five months after nephrectomy he received a renal transplant from his sister. Immunosuppression consisted of Prednisone 30 mg/day and Imuran 75 mg/day. Seven months post-transplant, surgical drainage and antibiotic treatment were required for a large left flank abscess which cultured *E. coli, Enterobacter aerogenes* and *Salmonella typhimurium. S. typhimurium* was also found in blood culture. A large right lower lobe lung abscess was noted on admission chest x-ray, however, no etiology was determined. Keflin and Gentamycin were administered for 14 days and he was discharged on Ampicillin. Immunosuppression was continued unchanged. One month later complaints of nonproductive cough, fever, headache and dizziness resulted in readmission. Purulent material was draining from the abdominal wound. Chest x-ray revealed the previously described right lung abscess as well as several new small cavitary lesions in the left lung. The flank abscess grew *Nocardia asteriodes, S. typhimurium, E. coli, Staphylococcal aureus* and *Bacteriodes oralis*. Five days after admission right thoracotomy with resection of the right middle lobe abscess was performed. Culture of the lung abscesses revealed *Nocardia asteroides* and *S. typhimurium*. Azathioprine was stopped and triple sulfonamides, Ampicillin, Clindamycin and Gentamycin were administered. Prednisone was maintained at 30 mg/day. A right transverse colostomy was performed because of feculent drainage in the left flank abscess. Postoperatively, transient mild right hemiparesis developed associated with increased left occipital tracer uptake on brain scan. Cerebral arteriogram, electroencephlogram and lumbar puncture were normal. Persistance of fever resulted in stoppage of all antibiotics except Ampicillin and sulfa. Fever gradually resolved and 3 months after admission he was discharged with a grossly normal chest x-ray.

Comment: Diagnostic thoracotomy was invaluable in this patient's management. Multiple bacterial pathogens in sputum cultures obscured

TABLE 2. *Mode of Diagnosis, Treatment and Outcome*

Case	Diagnosis Mode of	RX	Outcome	Cause of Death
1RH	Sputum	Gantrisin Ampicillin	Died	1. Diffuse bilateral nocardia pneumonia 2. Subarachnoid hemorrhage 3. Pneumococcal septicemia
2JD	Sputum	Ampicillin Triple Sulfa	Alive 3 years Post infection	
3VD	Sputum	Keflin, Kanamycin, Gantricin	Died	1. Diffuse bilateral nocardia pneumonia 2. Nocardia brain abscess
4JG	Bronchial Washings	Keflin, Kanamycin	Died	1. Right lung abscess (nocardia) extending into pulmonary artery. 2. Massive nocardia broncho-pneumonia
5LW	Sputum	Triple Sulfa, Ampicillin, Gentamycin, Cleocin	Alive.	
6JN	Sputum	Sulfadiazide Erythromycin Gentamycin Carbenicillin	Died	1. Fungal pneumonia 2. Gram-ve septicemia
7WC	Autopsy	————	Died	1. Acute MI 2° LAD thrombosis 2. Necrotising aspergillus pneumonitis
8CB	Sputum	Ampicillin, Keflin Kanamycin, Gentamycin	Died	Aspergillus pneumonia
9PED	Sputum	Amphotericin	Alive	
10FH	Sputum	Amphotericin Minocycline Septra	Alive	
11GB	CSF Sputum	Amphotericin	Died	Renal failure 2° chronic rejection and Amphotericin
12ED	CSF Sputum	Amphotericin 5-Fluorocytosine	Alive	
13TC	CSF	Penicillin, Keflin, Gentamycin	Died	1. Cryptococcal meningitis pneumonia 2. RUL cryptococcal abscess
14EG	Surgery	5-Fluorocytosine	Alive	
15GP	Autopsy	Gentamycin Carbenicillin	Died	1. Gram-ve septicemia 2. Candida pneumonia
16WP	Autopsy	Keflin, Gentamycin	Died	1. Candida bronchopneumonia 2. Pyelonephritis, gram-ve septicemia

and delayed diagnosis. Central nervous system involvement was presumed.

Case 10 had been treated for pulmonary aspergillosis (Fig. 3b) with intravenous Amphotericin B which was discontinued due to development of renal tubular acidosis. Two months later new pulmonary infiltrates and cavitation appeared (Fig. 3c). Gram stain and culture of bronchial washings revealed *Nocardia asteroides*. Treatment with triple sulfonamides was instituted. Imuran was discontinued while Prednisone was maintained at 40 mg/day. However, the lung lesions increased in size and open lung biopsy was performed. Biopsy specimens showed the nocardia to be resistant to triple sulfonamides, but sensitive to Septra and Minocycline. Therapy with these agents was successful with clearing of both chest x-ray and sputum (Fig. 3d). Imuran was then restarted at 25 mg/day.

Of the 5 deaths, 1 patient died following Amphotericin B treatment for cryptococcal meningitis and did not receive therapy for nocardiosis. Two other patients died 12 hours and 6 days respectively after admission without adequate therapy. The 2 remaining patients had nocardia diagnosed by sputum on the second and third hospital days respectively, and were treated with sulfonomides and Ampicillin or Erythromycin as well as cessation of Imuran and tapering of Prednisone, but showed progression of their pulmonary disease throughout their hospital course until their deaths.

Aspergillosis

Five patients had pulmonary aspergillosis and 2 of these patients had mixed infections with nocardia. One patient had aspergillosis located in the GI tract. All patients gave a 1 to 30 day history of fever, cough (often productive) and pleuritic chest pain. One patient had several episodes of hemoptysis 12 months prior to his final admission. His case is discussed below.

Case Reports

Onset of infection ranged from 1 to 4 months after renal transplantation. Chest x-ray showed infiltrates in 4 patients and left hilar cavitation in a fifth.

Diagnosis was made by sputum examination in 4 patients. In 1 patient diagnosis was made at autopsy. The patient died from myocardial

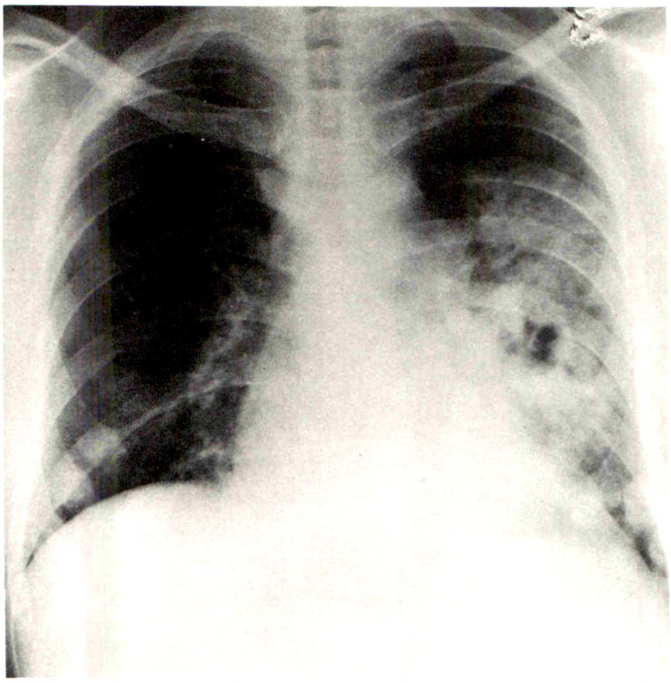


FIG. 1. Film is representative of Case 3 demonstrating pulmonary abscesses 2° to nocardia. Autopsy revealed diffuse pulmonary nocardiosis and two nocardial brain abscesses.

infarction 12 hours after admission. Sputum specimens in this case were negative.

Two patients survived. Case 9 developed pulmonary aspergillosis while hospitalized for treatment of threatened rejection (Fig. 4). Rapid diagnosis of aspergillosis by sputum examination was followed by a decrease in Prednisone to 50 mg/day and Imuran was discontinued. Treatment with intravenous Amphotericin B cleared both sputum and chest x-ray. However, transplant nephrectomy was required as a result of both the rejection episode and Amphotericin B therapy. Subsequently, he has undergone a second renal transplant and is now well 37 months after cessation of Amphotericin therapy. Case 10 (Fig. 3a) also had rapid sputum diagnosis and treatment with Amphotericin B. Immunosuppression was continued at previous levels. Amphotericin B was stopped when renal tubular acidosis developed. At that time the chest x-ray (Fig. 3b) had largely cleared but aspergillosis is still present in sputum. This patient is well 6 months after stoppage of Amphotericin B.

Three patients died and none received Amphotericin B. Case 7 died of a myocardial infarction as presented above. Case 8, a 47-year-old Caucasian man, underwent cadaveric renal transplantation in October of 1970 for chronic renal insufficiency secondary to systemic berylliosis. The patient had also suffered from respiratory insufficiency secondary to systemic berylliosis prior to his renal transplantation. Four months post renal transplantation, the patient had one episode of recurrent hemoptysis. Chest x-ray at that time revealed no active disease. Aspergillus was obtained on 8 occasions from the sputum culture. The patient received no treatment for this episode, which was felt at the time to be endobronchial aspergillosis. At the time of his final admission, 17 months post renal transplantation, the patient was receiving immunosuppression consisting of Imuran 50 mg/day and Prednisone 25 mg/day. Three weeks prior to his last hospital admission, the patient developed progressive dyspnea with cough productive of a thick yellowish, rusty sputum. This cough was accompanied by several episodes of shaking chills with temperatures of 99.5 to 101 F. The patient saw his local medical doctor for this cough and was placed on Ampicillin which he continued to take for the ensuing 3 weeks prior to his last hospital admission. The Ampicillin treatment did not improve his respiratory difficulty, and led to the patient's referral to Duke. On admission, the patient was moderately dyspneic. The temperature was 37.5 C. Blood gases revealed an arterial P_{O_2} of 28 with a P_{CO_2} of 27. The creatinine was 0.7 mg% and the bilirubin 2.1 mg%. Chest x-ray revealed bilateral lower lobe infiltrates. The patient's hospital course initially consisted of oxygen therapy and bronchial toilet. Because the diagnosis of pneumocystis was initially entertained, the patient was placed on Pentamidine. In addition, pending the arrival of culture results, the patient received Keflin and Kanamycin. The patient's sputum grew out Aspergillus. Sputum for pneumocystis was negative. The urine was negative for cytomegalovirus, bacteria and fungus. Multiple serological tests for histoplasma, blastomycosis and coccidioidomycosis were negative. The patient's hospital course consisted of gradual but progressive deterioration with increasing jaundice accompanied by failure of his pulmonary infiltrates to respond to his Keflin and Kanamycin therapy. Antibiotics were later changed to Gentamycin and Carbenicillin. Imuran and, later, Prednisone were discontinued. Pentamidine was discontinued after 7 days of therapy. Terminally, the patient's course was complicated with upper and lower GI

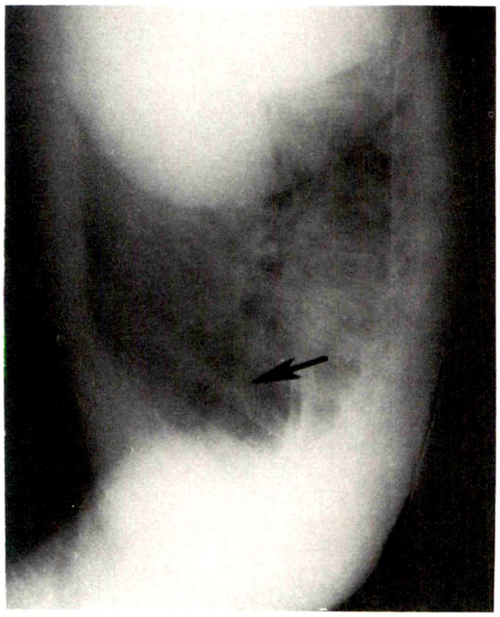
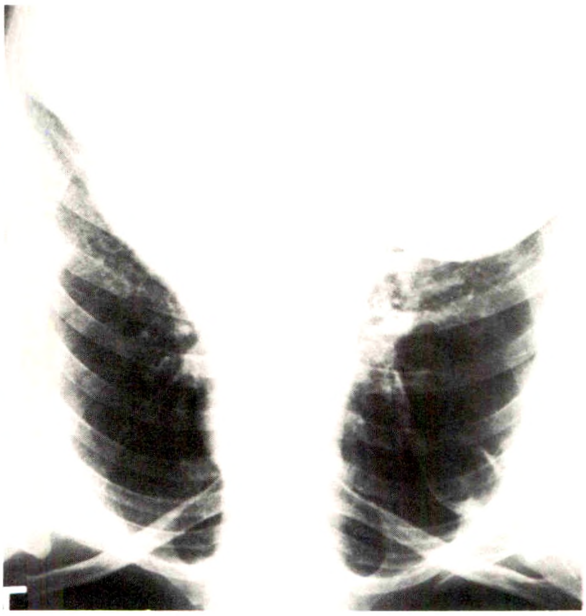


FIG. 2. X-ray film from Case 4 demonstrates a right upper lobe cavity of undiagnosed etiology. Five months later this abscess progressed to massive bilateral nocardial pneumonia and resulted in the patient's death.



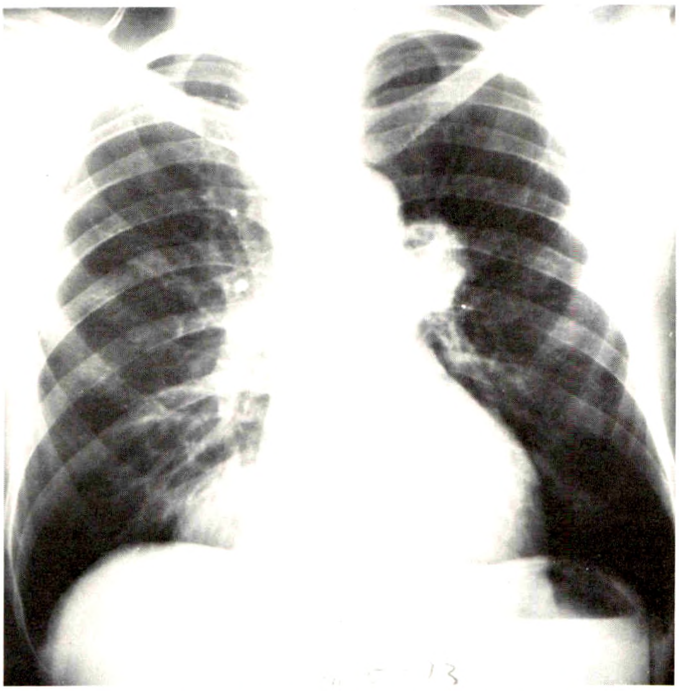


FIG. 3a. (Case 10) Chest film demonstrating a 5 cm diameter left, hilar lesion with areas of cavitation. Aspergillus was cultured from this patient's sputum.

bleeding peripheral vascular insufficiency and ischemic necrosis of his distal extremities. Renal function fell progressively. The patient suffered a respiratory arrest on April 4, 1972. Autopsy revealed aspergillosis in both his lungs and GI tract. Microscopic examination of the lungs in addition revealed multiple microscopic pulmonary vessel thrombosis, diffuse interstital fibrosis, edema and granuloma formation with intra-alveolar hemorrhage.

Comment: Endobronchial aspergillosis 3 months after renal transplantation was followed by disseminated aspergillosis 17 months after transplantation. Isolation of aspergillosis in sputum was not followed by Amphotericin B therapy.

Cryptococcosis

Four patients had pulmonary cryptococcal infections. One of these also had nocardia present in sputum and another had chromomycosis demonstrated in skin at autopsy. Central nervous system involvement by cryptococcus was demonstrated in 3 patients. Symptoms included headache, blurred vision and a fever in one, and headache, nausea, vomiting and cough productive of yellow sputum in a second. One patient was asymptomatic initially, but later relapsed and experienced fatigue and lassitude. A fourth patient was asymptomatic. The onset of infection was 5, 37, and 61 months post-transplantation in 3 patients. The fourth patient was found to have been infected at the time of surgery.

Chest x-ray revealed pulmonary infiltrates in 3 patients, pulmonary nodules in 2, and cavitation in one.

Diagnosis was made by culture or from stain of sputum and India ink examination of CSF in 2 patients, CSF alone in 1 and by surgery in the fourth.

Two patients survived. The first, Case 14, is a 35-year-old Caucasian man who underwent cadaveric renal transplantation in October of 1970. Postoperatively the patient was maintained on Imuran 00 mg/day and Prednisone 25 mg/day. Routine follow-up chest x-ray 37 months post transplantation revealed a solitary lung mass in the left lower lung fiel (Fig. 5). Tomograms showed the lesion to be non-calcified and multinodular.

The patient complained of no respiratory symptoms. He was afebril and examination of the chest was normal. Laboratory values showed WBC of 8,900, BUN of 11, and creatinine of 10. Sputum and urin cultures for bacteria and fungus were negative. Thoractomy with wedg resection of the lesion was performed. Biopsy revealed a granulom containing cryptococcus. Lumbar puncture was within normal limits Prednisone and Imuran were continued at preoperative levels throughout the hospital course. He received a 6 week course o 5-Fluorocytosine and has remained well at followup 6 months later.

Comment: An asymptomatic lung lesion was diagnosed 37 month post-transplantation and required surgical diagnosis.

The second survivor, Case 12, was found to have had pulmonar cryptococcosis at the time of transplantation and received 2 courses o Amphotericin B and 1 course of 5-Fluorocytosine. Prednisone wa tapered from 120 mg/day to 10 mg/day and Imuran was discontinued He remains well with a clear chest x-ray 28 months after discontinuatio of Amphotericin B therapy.

Two patients died; the first of whom (Case 11) had cryptococcu diagnosed by India ink preparation and spinal fluid culture soon afte admission. Immunosuppression consisted of Prednisone 100 mg/da and Imuran 75 mg/day. A right lower lobe infiltrate was also present o admission and sputum culture was positive for cryptococcus. Treatment consisted of 1500 mg of intravenous Amphotericin B over 1 weeks as well as tapering of Prednisone to 20 mg/day and discontinuation of Imuran. The right lower lobe infiltrate resolved; however, a abscess cavity appeared in the left upper lobe (Fig. 6). Serial ches x-rays showed clearing of this cavity and discharge chest x-ray reveale only minimal residual infiltrate. Discharge lumbar puncture was withi normal limits and sputum culture was negative for cryptococcus. However, renal function showed progressive decline with a discharg creatinine clearance of 21 cc/min. Over the 2 weeks following discharge

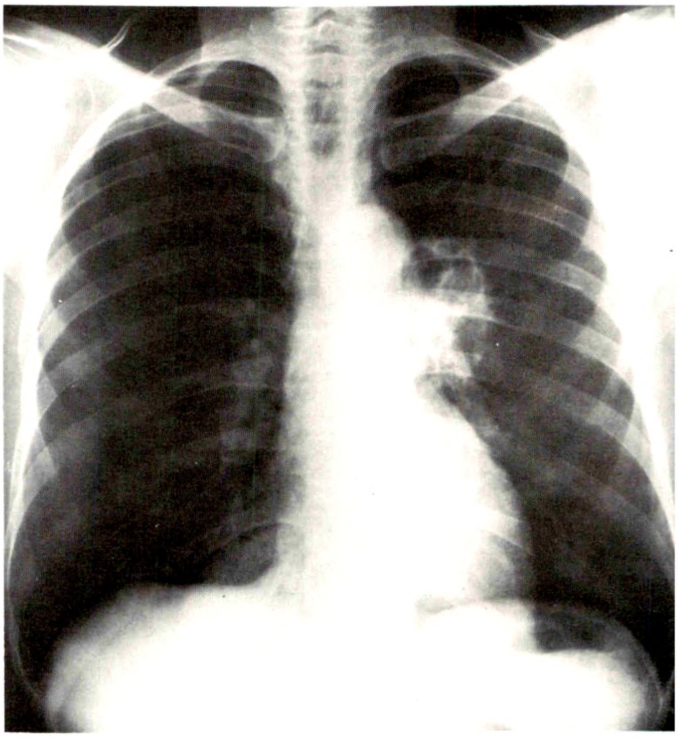


FIG. 3b. Followup film after treatment with Amphotericin B (405 mg) Marked clearing of the left hilar lesion is noted. Renal tubular acidosi forced discontinuation of Amphotericin treatment.

he became progressively weaker, stuperous and experienced nausea and vomiting. Readmission showed a clear chest x-ray and CSF within normal limits. BUN was 196 mg% and serum creatinine 4.5 mg% with a creatinine clearance of 10 cc/min. Prednisone was increased to 40 mg/day. The patient deteriorated rapidly, dying soon after admission. Autopsy was not obtained. Death was probably a result of chronic rejection and the nephrotoxic effects of Amphotericin B therapy.

The second death was Case 13, a 49-year-old man who received a cadaveric renal transplant in July 1967. Since that time he had been maintained on Imuran 100 mg/day and Prednisone 20 mg/day. Five years after transplantation, during evaluation of facial squamous cell carcinoma, routine chest x-ray revealed a right upper lobe lung infiltrate. He admitted to a 6 day history of cough productive of a yellow purulent sputum but denied chills or fever. Sputum culture revealed staphylococcus coagulase positive. Penicillin therapy resulted in marked clearing of the infiltrate and resolution of symptoms. However, a 1 x 1 cm right upper lobe nodule had been unmasked with a resolution of the infiltrate (Fig. 7). Sputum and gastric washings were negative for fungus. The patient was discharged on Penicillin; Imuran and Prednisone were continued unchanged. One month following discharge the right upper lobe nodule persisted unchanged in size and Penicillin therapy was discontinued. Two months following discharge he developed headache, nausea, vomiting and mild confusion resulting in readmission. Lumbar puncture revealed cryptococcus by India ink preparation and culture. Imuran was decreased to 25 mg/day and intravenous Amphotericin B therapy started. Prednisone was continued unchanged. Shortly after admission he became hypotensive. Blood and urine culture revealed *E. coli*. Keflin and Gentamycin therapy was started. Rapid deterioration in clinical condition ensued with dysuria and hypotension persisting. Death occurred on the seventh hospital day.

Autopsy revealed cryptococcal meningitis of the cerebellum and spine with cryptococcal invasion and necrosis of the cerebellar cortex. Budding yeast forms were present indicating failure of Amphotericin B therapy. Examination of the lung revealed that the right upper lobe nodule previously seen on chest x-ray consisted of demarcated but non-encapsulated area of necrosis with many cryptococci present within the lesion and adjacent alveoli. No objective evidence for *E. coli* septicemia was found.

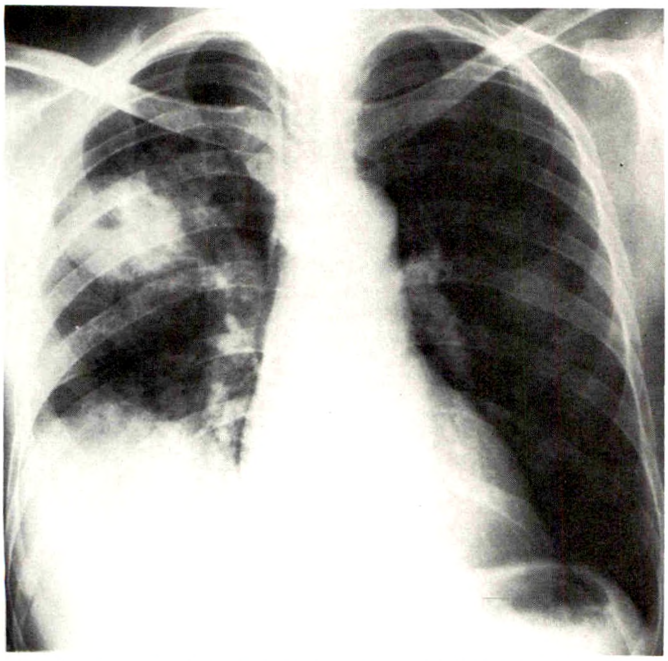


FIG. 3c. Reappearance of new pulmonary infiltrates and cavitation. Bronchial washings revealed nocardia asteroides which proved refractory to triple sulfonamide treatment and led to open biopsy allowing specific antibiotic sensitivities to be obtained.

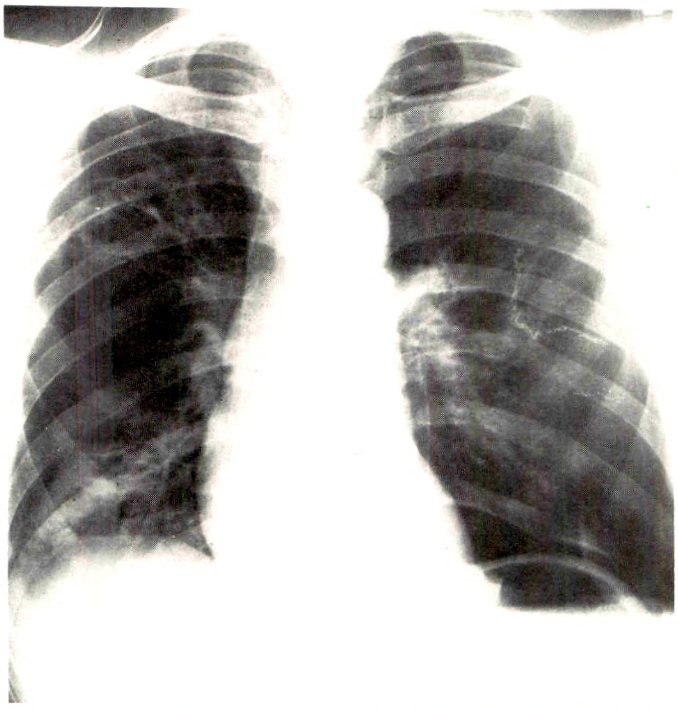


FIG. 3d. After two months treatment with Septra and Minocycline there is marked clearing of chest x-ray and sputum is now negative for nocardia.

Candida

Two patients had pulmonary candidiasis and both died. In each patient, candida was demonstrated only at autopsy. Case 15 developed right lower lobe cavitation while undergoing treatment for threatened rejection with massive doses of Prednisone, Imuran 50 mg/day and local graft irradiation within the first postoperative month. Autopsy revealed extensive candida bronchopneumonia which developed during treatment for a misdiagnosed rejection episode. Autopsy revealed an *E. coli* pyelonephritis as the cause of the deterioriation in renal function. No evidence of rejection was seen. Gram negative septicemia complicated each patients' terminal course.

Discussion

Rapid, accurate diagnosis of the responsible organism combined with determination of its antibiotic sensitivities is the cornerstone of management of any infection. This principle assumes added importance in the infected immunosuppressed renal transplant recipient.

Many of the same factors which render the renal transplant recipient susceptible to infection by opportunistic fungi are the same ones responsible for altering the clinical course and systemic response in the infected patient. These factors include antibiotic, steroid, and cytotoxic therapy as well as abnormal phagocytic activity, alterations in cellular and humoral immunity and the catabolism and acidosis of renal failure.[1,3,12,13]

Delayed cutaneous hypersensitivity is attenuated by both uremia and immunosuppression. Skin testing is not available for many of the fungal infections encountered

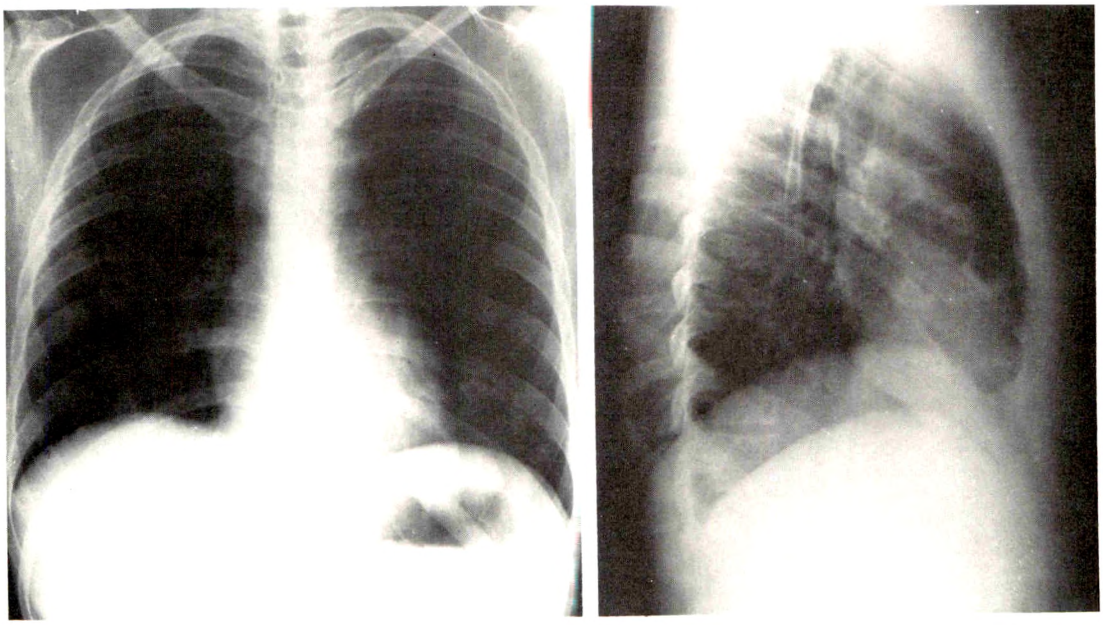


FIG. 4. (Case 9) Multiple pulmonary abscesses and cavities are present, best seen in lateral x-ray. Rapid diagnosis of aspergillosis by sputum culture allowed successful treatment with Amphotericin B.

and may be negative in the face of overwhelming infection.

Leukopenia, hyperglycemia, and moderate to severe renal failure were found by Adderson[1] to be consistently present among patients with fatal infections. Only one of our infections was associated with leukopenia at its onset. Three of the 18 patients in this series were receiving insulin at the time of infection. Leukocyte levels often relate more to the level of immunosuppressive drugs rather than the presence of inflammatory disease.

Interpretation of sputum cultures and their correlation with the clinical situation may be difficult at best. The organism isolated from the sputum may be the pathogen responsible for the clinical situation or it may represent only saphrophytic colonization of the respiratory tract.[24,26] This dilemma is illustrated by Case 8 in which investigation of hemoptysis 4 months post-transplantation resulted in isolation of aspergillus from sputum. In the face of an unchanged chest x-ray this was felt to represent saphrophytic colonization and was untreated. Sixteen months post-transplantation the patient developed fatal aspergillus pneumonia.

Stinson et al.[20] in a review of infectious complications following cardiac transplantation stated: "Because of the frequency with which mixed flora were cultured from sputum samples, the most valuable procedure in establishing the etiologic agent of pulmonary infections was percutaneous transtracheal aspiration." They also employed direct needle aspiration biopsy of pulmonary lesions in 3 patients in whom transtracheal aspiration failed to yield an etiologic agent. Two of 3 cases were diagnosed successfully in this manner before subsequent sputum and transtracheal culture yielded the offending organism. Transtracheal aspiration was responsible for yielding the etiologic agent in 1 of our cases (Case 2). Its more frequent use would appear to be indicated.

Several authors have emphasized the value of surgical diagnosis as a part of the aggressive work-up of these potentially fatal infections. Williams et al.[27] documented 3 patients in whom early extirpative therapy was both diagnostic and curative. Others have also excised localized areas of pulmonary fungal involvement in moribund patients with dramatic improvement.[4] All of our pulmonary fungal infections occurred in males. This

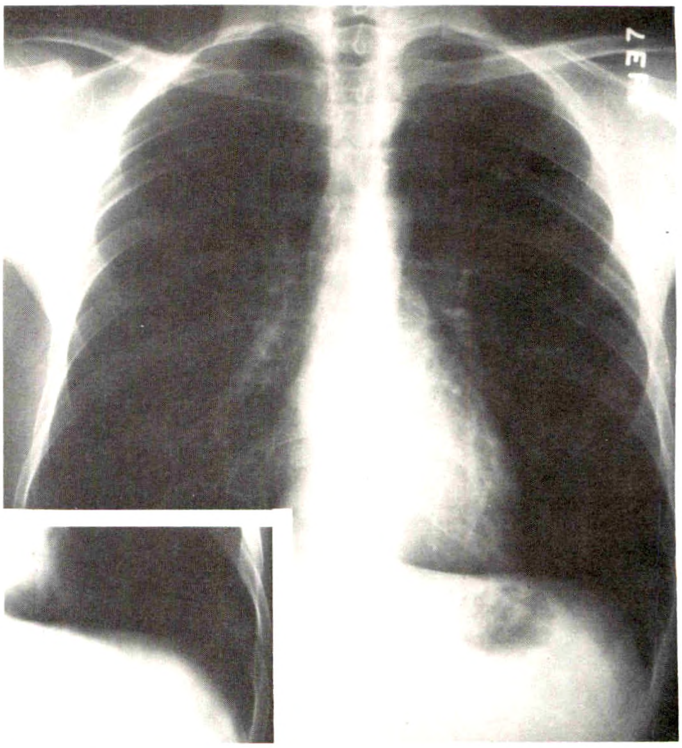


FIG. 5. (Case 14) Followup chest x-ray after transplantation demonstrated this solitary mass in the left lower lung field in an otherwise asymptomatic patient. At thoracotomy a cryptococcal granuloma was excised and appropriate therapy instituted.

sex predisposition has been noted by others.[9,16] No pulmonary fungal infections occurred in the HL-A identical group of renal transplants.

Many authors have noted that steroid and broad spectrum antibiotic therapy in man also increases susceptability to fungal infections.[3,12,13]

Steroid therapy increases susceptability of laboratory animals to fungal bronchopneumonias. The effects of cortisone on mice exposed to brief aerosols of aspergillus flavus spores included decreased peribronchial leukocytic infiltrate and early spore germination in comparison with non-cortisone treated controls.[7] Bach et al.[30] found that the frequency of fungal and nocardial infection increased linearly with the number of rejection episodes and their associated therapy. However, 8 of our 16 patients had no documented episodes of threatened rejections.

Cryptococcal pulmonary infections represented 5 of our 16 patients. This is a higher incidence than other series.[15,16,20,29,30] The reasons for this are not immediately apparent. Campbell[5] reviewed 60 normal hosts with untreated pulmonary cryptococcosis, and documented dissemination to the central nervous system in 7 of them. Two of our 4 patients had dissemination of cryptococcus from the lungs to central nervous system. In a third, both cryptococcal lung infiltrates and central nervous system involvement were documented simultaneously. Dissemination of this disease is more common in debilitating diseases[5,19] and has followed therapy with corticosteroids.[8,25]

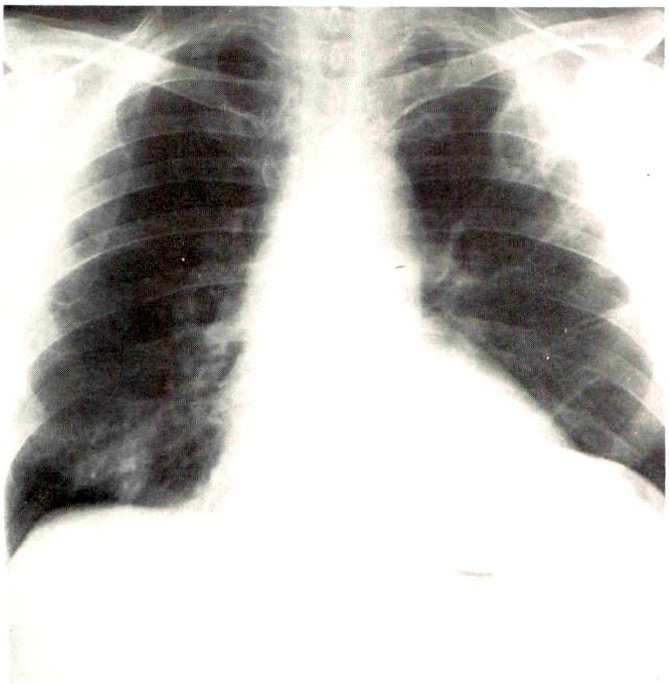


FIG. 6. Chest x-ray from Case 11 shows a right lower lobe infiltrate and an abscess cavity in the left upper lobe. The etiologic agent, cryptococcus responded to Amphotericin B with resolution of pulmonary pathology.

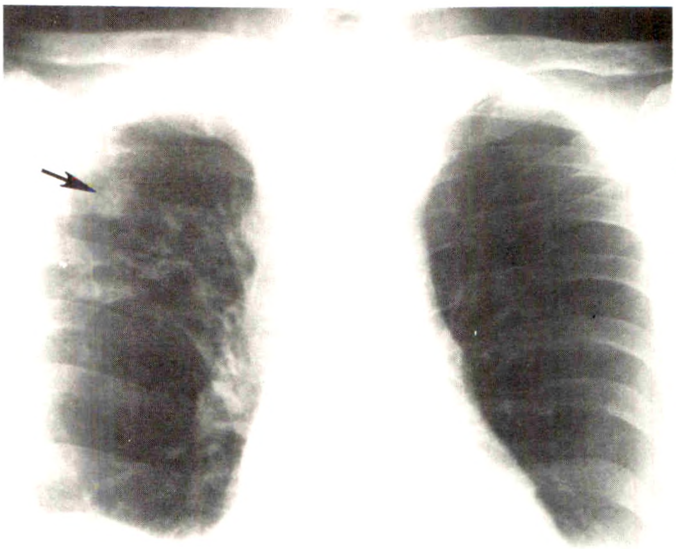


FIG. 7. PA chest x-ray demonstrating a 1 x 1 cm right upper lobe nodule. Two months later cryptococcal meningitis resulted in death. At autopsy, the pulmonary lesion proved to be a cryptococcal granuloma (Case 13).

Only 2 of our patients had candidiasis, a lower incidence than reported by others.[10,16,18] The routine prophylactic administration of oral Mycostatin in our hospitals may have played an important preventative role. The oral administration of Nystatin prevents candida overgrowth in the intestinal tract.[21] This may represent the organism's major point of entry. Stone[22] has recently presented evidence that thrice daily administration of oral Nystatin is uniformly effective in preventing evolution of Candida sepsis in a prospective randomized study of 243 burn patients.

Three patients (Cases 7, 15 and 16) in our series had no fungal organisms demonstrated prior to death. In 2 of these, early surgical diagnosis would have been of value in establishing the correct diagnosis and institution of appropriate therapy. The third patient died of myocardial infarction within 24 hours of admission. Sputum cultures were negative in this case.

Thoracotomy with lung biopsy was invaluable in determination of the pathogenic organism in 2 cases and in determining correct antibiotic sensitivity in a third case.

In the remaining 12 cases the organism responsible for the clinical situation was isolated from sputum of CSF. However, in 4 of these a significant delay in diagnosis occurred. Early surgical diagnosis in this group might have been of great benefit.

A high degree of suspicion is an important factor in the early diagnosis of these virulent fungal and nocardia infections. It should be emphasized that the symptomatic patient requires a greater sense of urgency than the asymptomatic patient with chest x-ray nodules or infiltrates. Failure of gram stain and culture of sputum for bacteria and fungus to reveal a pathogenetic organism or

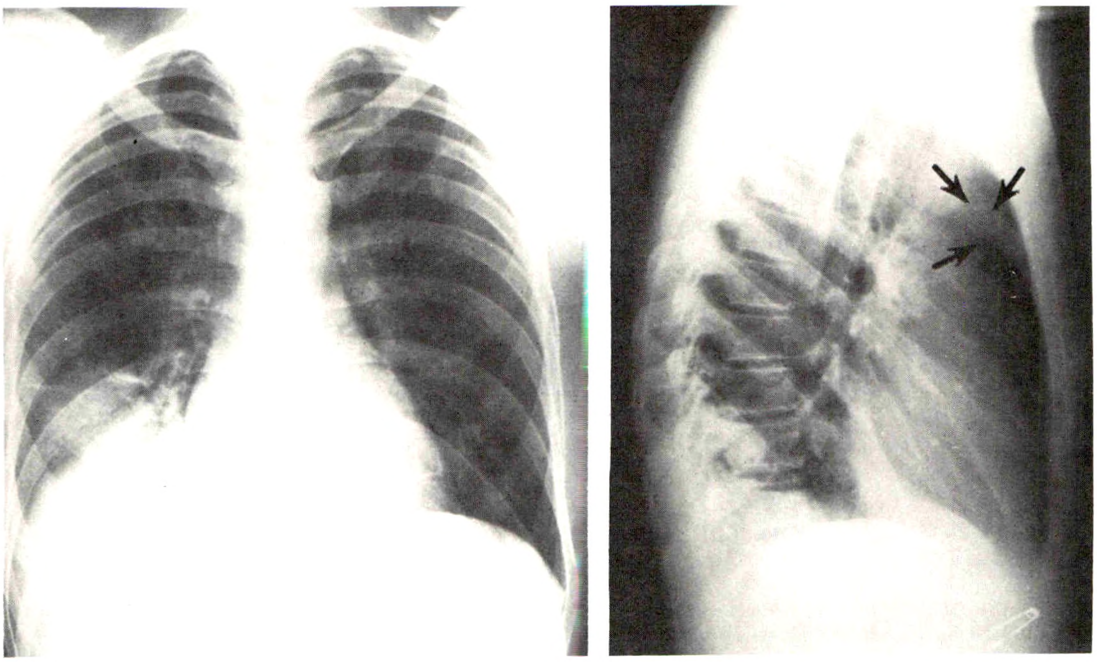


FIG. 8. Chest film from Case 6 demonstrating right lower lobe infiltrate and left upper lobe abscess. Nocardia and aspergillus were cultured from sputum. Death resulted from fungal pneumonia and gram negative septicemia.

failure to respond rapidly to indicated treatment should be followed by transtracheal aspiration and bronchoscopy for further specimen collection. Needle biopsy or thoracotomy should be performed if these tests are nonproductive. In both groups Imuran should be stopped and Prednisone tapered. Blood levels of appropriate antibiotics should be monitored.

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Metiamide:

An Antagonist of Histamine-Stimulated Gastric Acid Secretion

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Metiamide, 25 mg, antagonized the action of histamine on acid and pepsin secretion from both denervated pouches and innervated stomachs in dogs. In the same preparations its action on pepsin following food, pentagastrin or 2 deoxy-d-glucose was nonsignificant. Following pilocarpine or secretin, metiamide augmented pouch pepsin. The action of every acid stimulant was depressed by metiamide including the direct vagal action of deoxy-d-glucose on the innervated stomach. H_2 receptors seem, therefore, to be involved in some form in acid stimulated by the vagi, histamine, pentagastrin and pilocarpine. Pepsin stimulation does not seem to be via H_2 receptors with the exception of stimulation by histamine itself.

METIAMIDE is the second member of a new class of compounds capable of antagonizing histamine stimulation of the parietal cell.[3] Its ability to suppress pentagastrin-stimulated acid secretion has pushed the supporters of a physiological role for histamine in gastric secretion once more into a strong tactical position.[5,6] An obligatory role for histamine would be strengthened if metiamide were shown to antagonize cholinergic secretory stimuli, but so far this is uncertain.[2,3,5] The action of metiamide on pepsin secretion is not clear. Histamine is not usually invoked as an obligatory intermediate in pepsin secretion. Traditionally less attention has been paid to it, but superficially at least, the arguments seem equally valid for pepsin. Both histamine and gastrin may stimulate pepsin[9] and, in intact stomachs at least, those stimuli which increase acid also raise pepsin. Metiamide provides a tool by which intermediate stages in the stimulation of pepsin secretion can be studied.

Methods

Dogs with Heidenhain pouches and gastric fistulae were used. All weighed approximately 18 kg and were Retriever in type. Six was the maximum number used in any group of experiments and four the minimum.

The gastric stimuli used were pentagastrin,* 1 μg/min, pilocarpine nitrate, 40 μg/min, histamine phosphate, 10 μg/min, 2 deoxy-d-glucose, 10 mg/min, and secretin, 1 unit/min, all given by continuous intravenous infusion, and feeding (450 gm commercial dry dog food). These doses all produce acid secretion in the range of between 30 and 60% of the maximal secretion rate.

Metiamide,† 25 mg, was given as a single intravenous bolus when at least four collections had been made after the effect of the above stimulants had become apparent.

Samples were collected at 10 min intervals, by simple drainage from the fistula and by 10 min saline instillation and washout from the pouch. Acid was titrated in a Radiometer titrator and pepsin was determined by Anson's method.[1] Samples for pepsin determination more alkaline than pH 5 were acidified to pH 2 on collection.

For analysis the means of the acid and pepsin secretions per 10 min were calculated from the last three collections and compared with means calculated in the same way after metiamide. Significance of differences ($P<0.05$) was calculated as paired t using the Olivetti 602 and its statistical manual. All changes subsequently claimed have at least met this criterion. The figures give actual mean secretions for each control and experimental group and the means of the paired differences between pre- and post-metiamide means.

Results

Histamine (Fig. 1)

Metiamide clearly depressed histamine-stimulated acid and pepsin secretion from both pouch and fistula. His-

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*Peptavalon supplied by Ayerst Labs, Inc., Ft. Washington, Pennsylvania.

†Kindly supplied by J. W. Black, Smith Kline and French Ltd. Welwyn Garden City, Herts, U.K.

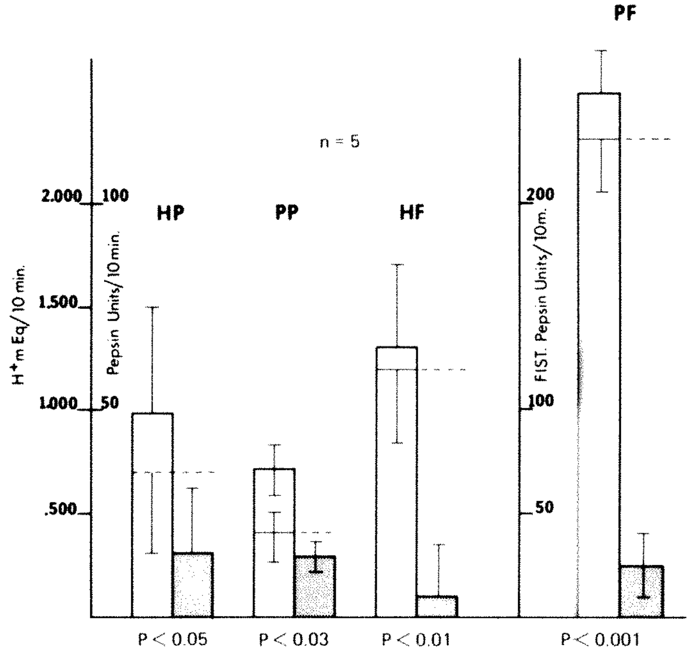

FIG. 1. Action of metiamide on histamine-stimulated acid (H) and pepsin (P) from Heidenhain pouches (P) and gastric fistulae (F). Bars are group means ± SEM before and after. The broken line represents the mean paired difference.

tamine, unlike pentagastrin, elevated pouch pepsin (compare Figs. 1 and 2).

Pentagastrin (Fig. 2)

Pentagastrin-stimulated pouch and fistula acid was significantly depressed by metiamide, but pepsin was not.

2 deoxy-d-glucose

Both pouch and fistula acid were stimulated by 2 deoxy-d-glucose, the former slightly and the latter strongly, since in it are combined both direct vagal and endogenous gastrin stimulation. The Heidenhain pouch is stimulated by gastrin alone. Metiamide depressed fistula acid. The action on pouch acid and on pepsin from both fistula and pouch was equivocal (Fig. 2).

Following 25 mg of metiamide a further 12.5 mg caused no further depression of acid secretion.

Pilocarpine (Fig. 3)

In these experiments the fistula collections were grossly contaminated with saliva and were, therefore, unreliable. Metiamide depressed pilocarpine-stimulated pouch acid. Pepsin was not depressed; indeed it showed a marginally significant increase.

Feeding

Pouch acid from fed animals was depressed by metiamide. Pepsin was unaltered.

Secretin

Metiamide augmented the increase in pouch pepsin produced by intravenous secretin. Fistula collections proved unreliable because of duodenal regurgitation.

Discussion

Metiamide depressed acid secretion whether stimulated by histamine, pilocarpine, pentagastrin or 2

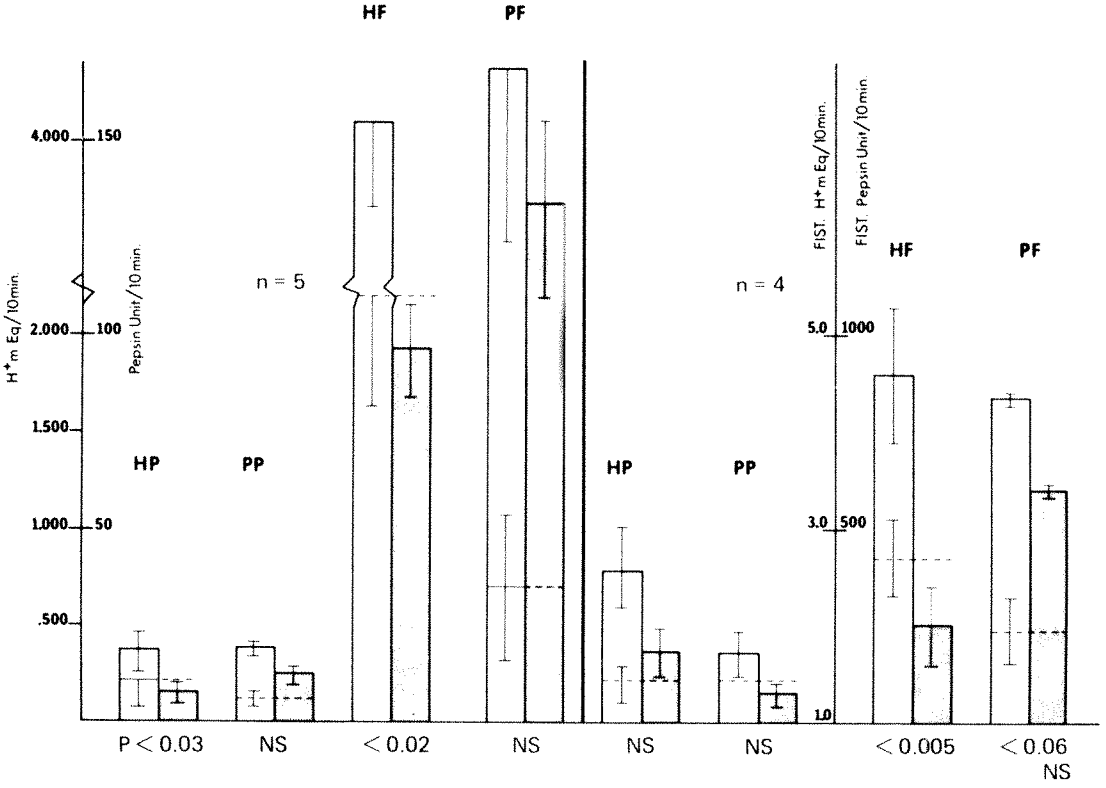

FIG. 2. (Left) Action of metiamide on pentagastrin-stimulated acid (H) and pepsin (P) from Heidenhain pouches (P) and gastric fistulae (F). Bars are group means ± SEM before and after. The broken line represents the mean paired difference. (Right) Action of metiamide on 2 deoxy-d-glucose stimulated acid (H) and pepsin (P) from Heidenhain pouches (P) and gastric fistulae (F). Bars are group means ± SEM before and after. The broken line represents the mean paired difference. NS = paired difference not significant.

deoxy-d-glucose. This was so from both pouch and fistula when they could be measured reliably, i.e., with the exception of fistula acid after pilocarpine and pouch acid after 2 deoxy-d-glucose.

Histamine stimulated pepsin secretion from both pouch and fistula. This is interesting in view of the fact that neither endogenous gastrin nor pentagastrin stimulate pouch pepsin.[4] This secretion was profoundly depressed by metiamide. The inhibition of pepsin following histamine was significantly greater than after any of the other stimuli.

In the pilocarpine and secretin experiments metiamide actually augmented pepsin secretion. It is clear that pepsin was not depressed by metiamide from the pouch after feeding or from the fistula after pentagastrin. The pouch pepsin responses after pentagastrin were equivocal as expected.[4]

2 deoxy-d-glucose acts on the main stomach both directly through the vagi and indirectly through vagally released gastrin. Since metiamide significantly depressed neither pentagastrin- nor pilocarpine-stimulated pepsin, it was hardly surprising that fistula pepsin was not significantly changed. What is surprising is that the trend was downward rather than towards augmentation which would have been expected from the pilocarpine experiments. In fact, this downward trend was uniform enough to lead to the expectation that with two more animals significance could be reached. The mechanism for this cannot be unravelled from the present data since the pure cholinergic stimulus we used (pilocarpine) produced contaminated fistula secretion and highly variable pepsin assays. The indirect gastrin effect on pouch acid, although undeniable, was too small to show significant depression in such a small sample (4 dogs).

These data would suggest that whatever the stimulus for acid secretion, an H_2 receptor is involved. Atropine depression and augmentation by ganglionic blocking agents have suggested an indirect gastrin or pentagastrin action to us via a muscarinic ganglionic mechanism culminating in an H_2 receptor.[8]

An H_2 receptor does not seem to be involved in the cholinergic or secretin stimulation of pepsin and seems to be an unlikely possibility in pentagastrin pepsin stimulation. Earlier work has shown at least two distinct mechanisms involved in pepsin secretion based on the failure of endogenous gastrin or pentagastrin to stimulate Heidenhain pouch pepsin and the contrasting success of cholinergics and secretin.[4] Histamine also can stimulate pepsin secretion from the denervated pouch but uniquely by way of a metiamide-sensitive receptor, thus suggesting a third mechanism.

Pepsinogens have been divided immunologically into two distinct classes.[10] Perhaps the receptors responsible for their secretion differ in their pharmacological characteristics. In the Heidenhain pouches the chief cells, one of the main sources of pepsinogen I, seem to be reduced in number and altered in appearance.[7]

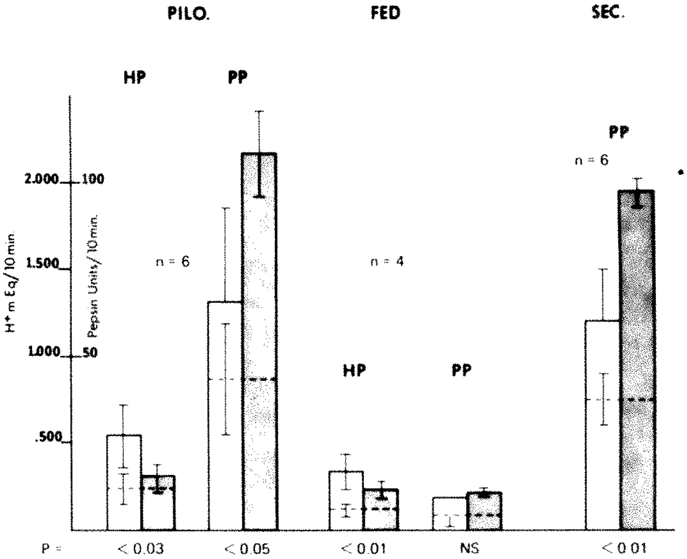

FIG. 3. Action of metiamide on pilocarpine- and food-stimulated pouch acid (HP) and pepsin (PP) and on secretin-stimulated pouch pepsin (PP). Bars are group means ± SEM before and after. The broken line represents the mean paired difference. NS = paired difference not significant.

Acknowledgment

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Principles in the Management of Arterial Injuries Associated with Fracture/Dislocations

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Ten out of 355 patients admitted with fracture and/or dislocations of long bones secondary to blunt trauma had associated vascular injuries. The clinical recognition of the associated vascular injury and its verification by arteriography, Doppler study or surgical exploration resulted in early vascular repair and limb salvage. The controversial aspects of bone stabilization followed by vascular repair versus primary vascular repair, skeletal traction and delayed internal fixation together with fasciotomy-fibulectomy are discussed. Our results with the injuries seen justify the principle of bone stabilization followed by vascular repair, particularly since a team effort resulted in little time lost prior to circulatory restoration. The problems following vascular repair-namely anterior compartment syndrome, acute renal failure and cardiac arrest are presented with their principles of management.

THE EXCEPTIONALLY HIGH amputation rate in acute traumatic arterial injury during World War II was the stimulant for surgeons during the Korean War to perform direct arterial repair and realize a reduction in amputations from 49.6% to 10.8%.[3,8] Depending upon the site of an acute arterial injury, however, the amputation rate may still be high. Thus failure to repair a damaged popliteal artery will usually result in loss of the extremity; whereas arterial injury even when associated with a fracture about the elbow rarely requires amputation.[6,7,11,13,19] The association of arterial injuries with fracture or dislocation secondary to blunt non-penetrating trauma has been a relatively uncommon event. Effective management in these combined injuries requires recognition of the arterial injury without delay and appropriate orthopedic management of the fracture or dislocation. Injuries to other body systems may be so severe they take precedence over the vascular trauma or cause it to go unrecognized. A high index of suspicion of arterial injury should exist whenever arteries are in close proximity to bone and held in a semi-fixed position.[10] The arteries most frequently involved are the subclavian artery beneath the clavicle, the brachial artery adjacent to the humeral shaft and supercondylar portion of the humerus, the femoral artery near the femoral shaft, and especially the popliteal artery as it is stretched across the popliteal space with both superior and inferior fixation. Since experience with the management of this complex problem is limited,[1,4,9,14,15,18,20] due to the infrequent combination of arterial and orthopedic injury, we felt a review of the problems posed in the diagnosis and treatment of these lesions was appropriate.

Clinical Material

From August 1, 1968 to July 31, 1974, 16,931 orthopedic emergencies were seen at the Framingham Union Hospital and 1,702 patients required hospital admission. From this latter group 355 patients had traumatic fracture of the long bones with or without associated dislocation of the respective joint. There were 233 males and 157 females. Ten patients, all males, had associated arterial injuries for an incidence of 0.28%. Their ages ranged from 18-46 years with a mean of 25 years. Whereas the lower extremity was the most common site of injury, three patients had injuries involving the upper extremity (Table I). All patients suffered non-penetrating blunt trauma and in three patients the blunt force was so great it produced a compound fracture thereby resembling a penetrating injury.

All injuries were the result of vehicular accidents, six motorcycle and three automobile; while one patient sustained his injuries from a fall of several feet (Table 2). Surgery began within 8 hours from arrival in the Emergency Ward, an average of only 3½ hours being used in resusitation and/or diagnostic delay. The time from injury to arrival in the Emergency Ward was not recorded in these patients. Arteriography was employed in 6 patients preoperatively, while in recent years the Doppler flow study was used to support or establish the diagnosis of arterial occlusion in three patients. In all patients the diagnosis was suspected by the clinical signs of arterial ischemia together with the absence of peripheral pulses.

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TABLE 1. *Arterial Injury Associated With Fracture and/or Dislocation.*

Orthopedic cases seen in ER		15,931
Admissions from ER		1,702
Patients with long bone fracture and/or dislocation		355
Male	233	
Female	157	
Associated arterial injury with long bone fracture and/or dislocation		10
Male	10	
Female	0	
Ages	18-46 (mean 25)	
Site of injury		
Lower Extremity	7	
Upper extremity	3	

In one patient, Case 2, peripheral pulses were always present but the sudden onset of shock and hemothorax 10 days following admission led to emergency exploration and the diagnosis of subclavian vein laceration secondary to the piercing of this vein by a fractured 1st rib segment. Pulses were restored in all but one patient (Case 6). In this latter patient a more vigorous attempt to restore pulses was abandoned when no clots could be retrieved from the distal tree and the hand was observed to be warm with good capillary refill.

Arterial ischemia was the result of intimal tear and secondary thrombosis in 5 patients, contusion and thrombosis in two patients, and angulation with entrappment of the vessels by the fracture in two patients (Table 3). The latter two patients required no vascular procedure but had restoration of peripheral pulses when the fractures were reduced and stabilized. Arterial continuity in the remaining patients was obtained by resection of the traumatized area and primary repair (2) or by autogenous vein grafts. (5) Four of the 7 patients requiring vascular repair had distal thrombi extracted by the Fogarty catheter with resultant brisk back flow bleeding. In one patient the vascular injury was a venous laceration and this was controlled by primary venorrhaphy.

Internal fixation was employed as the primary method of management in 6 patients, reduction and casting in 3, and in the one patient with over-riding 1st rib fracture, the rib was resected in order to control the acute vascular accident (Table 4). Three patients whose injuries involved the knee joint had temporary footdrop, all with recovery and a good functional result; whereas one patient who developed an anterior compartment syndrome had a permanent footdrop. A below knee amputation secondary to muscle necrosis and infection was required in one patient; however, his final functional result with a prosthesis was excellent. One patient with brachial plexus avulsion and subclavian artery occlusion had a flail arm and is classified as a poor result.

Discussion

Arterial injuries associated with fractures or dislocations are immediate or delayed. The immediate complications are: 1) Laceration of the vessel, either partial or complete, 2) Occlusion, either partial or complete, which may be due to (a) angulation, (b) extrinsic compression, (c) intimal tears and disection with an intact adventitia, (d) stretching and (e) spasm. The delayed complications are: 1) False aneurysms, 2) AV fistula, 3) Thrombosis of the vessel following reconstructive surgery, 4) Ischemic muscle contractures. For successful management of a patient with a combined vascular-orthopedic injury the recognition of circulatory compromise is indispensible. Poor results are not due to a more severe injury or one which is less amenable to surgery, but to procrastination and failure to appreciate signs and symptoms of arterial insufficiency when they accompany a fracture or dislocation. Valuable time has been lost by temporizing with ancillary measures such as sympathetic nerve block, anticoagulation, and fasciotomy as primary treatment. The safe time lag of 6-8 hours advocated by Miller and Welch[12] is arbitrary since adequate collateral circulation provides a longer safe period and may account for the lower incidence of limb loss following injury about the elbow joint as compared to the knee joint when treatment is either inadequate or delayed. While the time from injury to surgery in our series was not recorded the delay from arrival to surgery was well within the safe limit and may account for our good overall result. The findings of arterial ischemia when associated with a history of bleeding or a pulsating mass is diagnostic. On the other hand, if the foot or hand is cool rather than cold, hypoasthetic rather than anesthetic, pale rather than ashen, the diagnosis is more difficult especially when an operation will convert a closed fracture into an open one with the potentials for osteomyelitis. Such a state may exist with reflex arterial spasm; however, complete anesthesia or small muscle paralysis is rare and the effect of this reflex vasospasm is diminished with the relief of pain, splinting of a fracture, or intra-arterial Papaverine. If, however, the spasm is not relieved, excision and reanastomosis of the ends or interposition with a graft is the procedure of choice. Extrinsic mechanical factors also cause the signs and symptoms of arterial ischemia as experienced in Case 7. It is to this group that arteriography or Doppler study is helpful and may prevent unnecessary surgery. Diminished or absent Doppler sounds or pulse waves support the diagnosis and lessen the need for arteriography; however, if doubt exists and the patient's condition is stable, arteriography or exploration should be performed. If gentle closed reduction of a dislocation or fracture fails to immediately improve circulation, arteriography or exploration should be done without delay. Arteriography should be used prior to or during any re-exploration, and upon completion of a repair to exclude technical errors which may lead to subsequent failure. While arteriography establishes the exact location and extent of arterial damage or extrinsic cause for pulselessness, it is a

TABLE 2: *Preoperative Vascular Evaluation.*

Cases	Age(yrs)	Cause of Injury	ER to OR Time	Arteriography Preoperatively	Doppler	Preop Pulse	Postop Pulse
1. BD	38	Fall	1 Hour	None		Absent Brachial Radial	Strong Brachial Radial
2. TD	21	Auto	10th day bleed ICU to OR time 2 hours	None	None	All palpable upper extremity	All palpable upper extremity
3. FP	26	Motorcycle	5.25 hrs.	Superficial femoral occlusion at fracture site; no run off	None	? DP	Strong Popliteal PT DP
4. BD	19	Motorcycle	Unknown, transfer from elsewhere.	Peroneal artery patency other vessels not seen	None	Absent	Strong DP
5. JL	21	Auto	4.5 hrs.	Popliteal occlusion-collateral reconstruction of peroneal artery	None	Absent Popliteal PT DP	Strong Popliteal PT DP
6. CK	24	Motorcycle	7 hrs. 47 min.	Subclavian artery occlusion distal to internal mammary branch-minimal reconstruction of axillary artery	None	Absent Brachial Radial	Absent Brachial Radial
7. DM	19	Motorcycle	4 hrs.	Anterior tibial narrowing at fracture site, visualized posterior tibial to ankle	None	Absent PT DP	Strong PT DP
8. JS	19	Motorcycle	7.5 hrs.	Popliteal occlusion with intraluminal thrombosis, reconstruction of trifurcation.	Absent pedal & Popliteal sounds	Absent Popliteal PT DP	Strong Popliteal PT Absent DP
9. EB	18	Motorcycle	1 hr. 50 min.	Not done	Absent pedal sounds	Absent PT DP	Strong PT DP
10. GI	46	Auto	1.25 hrs.	Not done	Absent pedal & Popliteal sounds	Absent Popliteal PT DP	Strong Popliteal PT DP

TABLE 3. *Arterial Injury and its Management.*

Cases	Vascular Injury	Repair	Morbidity	Vascular Result
1. BD	Intimal tear and thrombosis brachial artery, Contusion 4 cm long	Resection and cephalic vein graft	None	Restoration of all pulses
2. TD	Laceration right subclavian	Primary suture repair	None	Good—No venous occlusion
3. FP	Intimal tear popliteal artery & thrombosis, Contusion 3.5 cm long, Transection of popliteal vein	Resection of artery and saphenous vein graft. Primary anastomosis of vein.	None	Restoration of pulses. No venous insufficiency.
4. BD	Occlusion of anterior and posterior tibial arteries by angulation, compression and entrapment	None—Reduction and stabilization of fracture	Muscle necrosis and infection	Restoration of DP pulse
5. JL	Contusion & thrombosis of popliteal artery 2.5 cm long	Resection & saphenous vein graft	None	Restoration of pulses
6. CK	Intimal tear & thrombosis left subclavian artery, Contusion 2 cm long	Resection & end to end anastomosis	None	Poor—Pulses remained absent but arm & hand warm with good capillary refill
7. DM	Angulation of anterior and posterior tibial arteries	None—Reduction and stabilization of fracture	None	Restoration of pulses
8. JS	Intimal tear & thrombosis of popliteal artery, Contusion 5-7.5 cm long	Resection and saphenous vein graft, subcutaneous fasciotomies	None	Restoration of pulses
9. EB	Intimal tear & thrombosis of popliteal artery, 3.5-4 cm long contusion	Resection & saphenous vein graft, subcutaneous fasciotomies	Anterior compartment syndrome	Restoration of pulses
10. GI	Contusion & thrombosis of superficial femoral artery 2.5 cm long	Resection & end to end anastomosis	None	Restoration of pulses

double-edged sword in that it is time consuming and the delay may prove critical to limb survival.

Once a diagnosis is established the first question to be answered is whether or not the limb is salvageable. Extensive tissue destruction resulting in a functionless or useless extremity should undergo primary amputation

TABLE 4. *Orthopedic Management, General Morbidity and Final Functional Result.*

Cases	Orthopedic Injury	Repair	Result	Morbidity	Final Functional Result
1. BD	Comminuted supracondylar fracture left femur	Bar bolt & Rush rod	Good	No orthopedic or vascular	Good
	Fracture right femur	Intramedullary rod	Good	Diabetes Insipitus	
	Fracture right humerus	Intramedullary rod	Good		
	Fracture right radius	Plate & screws	Good		
	Fracture right shoulder	None	Good		
2. TD	Fracture left femur	Intramedullary rod	Good	Laceration right subclavian vein	Good
	Fracture 1st rib	Resection of 1st rib	Good		
3. FP	Comminuted supracondylar fracture of left femur	Compression plate	Good	Temporary footdrop	Good
4. BD	Comminuted fracture proximal 1/3 tibia & fibula	Kirschman Rods & cast	Poor	Muscle necrosis requiring BK amputation	Good with prosthesis
5. JL	Dislocation left knee	Reduction & cast	Good	Temporary footdrop	Good without brace
6. CK	Fracture transverse process T, fracture left pubic ramus	None	Poor	Avulsion brachial plexus	Poor—flail arm
7. DM	Fracture tibia and fibular distal 1/3	Reduction & cast	Good	None	Good
8. JS	Posterior dislocation left knee	Reduction & cast	Good	Temporary footdrop	Good
9. EB	Comminuted posterior displaced fracture of proximal tibia	Reduction, internal screw fixation	Good	Anterior compartment syndrome	Fair—permanent footdrop requiring a brace
10. GI	Fracture left femoral shaft	Compression plate	Poor	Angulation of fracture site & compression plate requiring delayed rod fixation	Good

with or without immediate postoperative prosthesis. If salvage seems possible avoid unnecessary delay. Following proximal and distal arterial control, the fracture is stabilized thereby safeguarding vascular repair. In challenging this standard approach, Connolly[2] has demonstrated that the disruptive resistance of a typically sound vascular repair to longitudinal traction is greater than a 40 pound pull. The infrequency with which the fracture spears or disrupts the anastomosis versus the reality of increased operating time, higher infection rate, and further disruption of collateral circulation in an already severely tramatized limb has led to the recommendation of primary vascular repair and skeletal traction for stabilization followed by delayed internal fixation 1-2 weeks after initial therapy.[16,17] This approach seems acceptable for contaminated wounds, war injuries and prolonged delays prior to initial therapy, but in the community practice when most injuries are closed, uncontaminated and seen early, the standard approach of internal fixation followed by vascular repair has provided good results and with little time lost.

The traumatized vascular structures should be adequately debrided to assure normal arterial structures for reconstruction. Repair may be in the form of 1) Lateral suture, 2) Venous patch graft, 3) Resection with end to end anastomosis, 4) Restoration by interposed autogenous reversed saphenous vein graft or synthetic dacron grafts, 5) Re-attachment of the intima if the tear is circumferential and 6) Bypass grafting about the area of trauma to relatively uncontaminated tissues. The distal arterial tree should be perfused with a Heparin solution and the graft placed under slight stretch. All clots should be removed with a Fogarty catheter or, if not available, by antegrade and retrograde flush prior to completion of the reconstruction. Completeness of this part of the procedure should be checked with operative arteriography. All major veins are repaired because without adequate venous return the already elevated tissue pressure by the edema and bleeding from the bone and soft tissues will be further increased and with time the resultant damage would be equivalent to that produced by direct interruption of a major artery. Subcutaneous fasciotomy of adequate length and extent has been advocated by some authors in all patients with traumatic injury; whereas others believe both fascia and skin must be incised or fibulectomy performed to prevent the anterior compartment syndrome.[5] Simple elevation of the limb above heart level postoperatively is helpful and possibly a preventative that should be carried out in all patients. Aggressive immediate re-exploration of the artery with or without arteriography is mandatory if signs of ischemia re-appear. Patients with prolonged delays prior to surgery or who have had tourniquets applied for the control of bleeding may develop postoperative renal failure secondary to the liberation and absorption of myoglobin and other tissue breakdown products or cardiac arrest due to the release and absorption of large amounts of potassium. Manitol and good hydration preoperatively, intraoperatively, and postoperatively may help prevent these complications.

AV fistula, a late complication, is treated by excision and restoration of arterial and venous continuity rather than quadruple ligation; whereas a false aneurysm or a nonessential artery may be treated by proximal arterial ligation, but when the artery must be preserved vein bypass grafting well removed from the site of the lesion is preferable.

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Biliary Cysts

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This review brings the total number of biliary cysts reported in the world literature to 955. Eighty-one per cent of patients are females and 61% were discovered before age ten. The classical triad of right upper quadrant pain, right upper quadrant mass, and jaundice is present in 38% of cases. The duration of symptoms prior to diagnosis ranged from less than one week to more than 40 years. The etiology is multifaceted and evidence of the existence of both acquired and congenital cysts is presented. The most useful diagnostic tool is fiberoptic endoscopy with retrograde contrast injection of the common bile duct and pancreatic duct. The incidence of biliary carcinoma in patients with biliary cysts is found to be 2.5%; 24 cases have been reported. Considerable controversy has existed concerning the best operative procedure for biliary cysts; no treatment or medical treatment yielding a 97% mortality rate. In an analysis of 235 patients presented since 1968 with an average followup of 5.2 years, the best procedure appears to be excision with either choledochocholedocostomy or Roux-en-Y hepaticojejunostomy. The operative mortality for all procedures is now 3 to 4%.

CYSTIC DILATATIONS of the biliary tree have been reported in many forms and by far the most common location is the common bile duct, or choledochus, hence the term choledochal cyst. Although Vater[1] is often cited as reporting the first case in 1723, the first well documented case was reported by Douglas[2] in 1852 in which he presented a biliary cyst in a 17-year-old girl. By 1909, Laverson[3] had collected 28 cases and Waller[4] presented 35 cases in 1917. Following these reports were series by McWorter (1924),[5] Seneque and Tailhefer (1929),[6] Zinninger and Cash (1932),[7] Clarke (1932),[8] Gross (1933),[9] Yotsuyanagi (1936),[10] Walton (1939),[11] Bangerter (1941),[12] and Poate and Wade (1941).[13] In 1943, Shallow, Eger, and Wagner[14] collected from the World's Literature 182 cases of which they felt 175 cases were authentic enough to be included in their report. In 1956, Tsardakas and Robnett[15] added 67 cases to bring the total to 242. By 1959, another 161 cases were presented by Alonso-Lej[16] for a total of 403 cases. Lee[17] brought the total number of cases in the World's Literature to 500 by adding an additional 97 cases in 1969. Since Lee's report, no complete reviews have been published. Between 1969 and February 1975, 451 new cases have been reported[18–37,39–46,48–139] and an additional four cases are briefly presented in this review. Since the publication of Lee's study in 1969, new theories of etiology have been proposed, new types of biliary cysts or dilatations have been described, new diagnostic methods have been developed, and additional information regarding operative management is now available and are discussed in this report.

Case Report

R. J., a 33-year-old Caucasian man, underwent cholecystectomy for right upper quadrant pain in 1965. At the time of operation, no abnormalities of the common bile duct were noted. His post-operative course was unremarkable.

In 1966 he had intermittent pain similar to that he had experienced one year previously. No masses were palpated on physical exam. Serum alkaline phosphatase was normal and serum bilirubin was 2.6 mg%. An upper gastrointestinal series was normal, but two separate

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TABLE 1. *Tabular review of the four new cases presented in this report:*

Patient	Age, Sex, Race	P†, M†, J†	Duration of Symptoms	Type of Cyst	Operation and date	Complications	Date Last Followup
M. R.*	41 yr, M, C‡	+ − −	?	I	1.CCD April, 1956	Cholangitis	
					2. RYCCJ Feb. 1971	Intermittent Cholangitis	Feb., 1975
T. R.	4 mo, F, N	− + +	1 mo	I	1. CCD Feb. 1973	Doing Well	Feb., 1975
J. M.	9 yr, F, C	− + +	1 mo	I	1.CCD July 1969	Doing Well	Feb., 1975
R. J.	33 yr, M, C	+ − −	1 day	None	1. Cholecystectomy March 1965	RUQ Pain	
				I	2. CCD Aug. 1966	Jaundice RUQ Mass	
					3. RYCCJ April 1973	Jaundice RUQ Mass	
					4. Revision RYCCJ May 1974	Adenocarcinoma, Cholangitis Gastric Outlet Obstruction	
					5. Gastrojejunostomy July, 1974	Died, July, 1974 Cholangitis and Sepsis	
R. S.	47 yr, M, C	+ − +	6 yr	I	1. Excision with RYHS Feb. 1975	Doing Well	Feb., 1975

*Previously Reported[18]
†PMJ = Pain, Mass, Jaundice.
‡Caucasian, Negro

CCD = Choledochocystduodenostomy
RYCCJ = Roux-en-y choledochocystjejunostomy
RYHJ = Roux-en-y Hepaticojejunostomy

intravenous cholangiograms failed to visualize the biliary tree. The diagnosis of common bile duct stone was entertained and the patient was taken to surgery. At the operating table, a 6 cm by 6 cm Type I biliary cyst was found which involved the extrahepatic biliary tree. The lack of involvement of intrahepatic biliary radicles was shown on an operative cholangiogram. The second portion of the duodenum was opened and explored and no Type III lesion was found. Clear fluid (probably pancreatic juice) was seen coming from the ampulla of Vater, but no bile could be seen coming from the ampulla. Green bile, however, was present in the nasogastric aspirate, but no gastrobiliary fistula could be demonstrated by contrast roentgenology at the operating table. Three small stones were removed from the common bile duct cyst and a standard choledochocystduodenostomy (CCD) was performed. Postoperatively the patient did well.

When seen in 1973 the patient had clinical signs of jaundice and a right upper quadrant mass. The diagnosis of obstructive jaundice was made and at operation a firm mass was found in the porta hepatis. A Roux-en-Y choledochocystjejunostomy (RYCCJ) was fashioned. No biopsy was taken.

In 1974 the patient again had obstructive jaundice and underwent revision of the RYCCJ with Y-tube drainage. The same firm mass was palpated and biopsy revealed well differentiated infiltrating adenocarcinoma of the common bile duct. The patient did well postoperatively but returned in June 1974 with a gastric outlet obstruction secondary to an extrinsic mass-lesion. This was felt to be secondary to the biliary carcinoma and a palliative gastrojejunostomy was performed. With the exception of a bout of cholangitis, he did well postoperatively only to return one month later with recurrent gastric outlet obstruction, obstructive jaundice, dehydration, cholangitis, and septic shock which resulted in his demise.

Three additional new cases and the above case are presented in Table 1. They have only been included for their statistical value since they contain no unique findings. Additional followup on a previously reported case M. R.)[18] is also included in Table 1.

Pathology

Originally three types of biliary cysts were described. Tsardakas[15] termed Type I "congenital cystic dilatation of the common bile duct." In Type I, there is usually a distal narrowing of the common bile duct with the cyst proximal to the point of narrowing. Occasionally the common bile duct distal to the cyst is found to be normal. The remainder of the biliary tree is usually normal, however, this is not always so. The cystic dilatation may extend into the hepatic ducts and into the intrahepatic biliary radicles. The cystic duct may enter the cyst or may enter a normal common bile duct proximal or distal to the cyst. A Type I cyst may on occasion extend distal to the junction with the pancreatic duct.[20] For the sake of comparison, the format used by Saito[19] is followed here, and thus, all cases in which there is diffuse dilatation of both intrahepatic and extrahepatic ducts are included in Type I cysts.

Type II is actually a common bile duct diverticulum usually arising laterally. Type II, or choledochocele, is a dilatation of the intraduodenal portion of the common bile duct and is often associated with duodenal obstruction.

In 1939, McWorter[149] described the association of

TABLE 2. *Age of Patients at time of diagnosis (820 Cases).*

< 1 yr	1-10 yrs	11-20 yrs	21-30 yrs	> 40 years
25%	35%	16%	15%	8%

multiple intrahepatic biliary cysts with multiple Type II cysts. Since that time, a total of 32 cases have been reported[20] in which there is an association of intrahepatic with extrahepatic biliary cysts. Also intrahepatic biliary cysts have been described in the absence of extrahepatic cysts. These intrahepatic cysts can occur as an isloated lesion or associated with polycystic disease or congenital hepatic fibrosis. In 1958, Caroli[151] reported the association of intrahepatic and extrahepatic biliary cysts and often this type is called Type IV, or Caroli's disease. In this report, all cases of multiple cysts, regardless of shape and location, are classified as Type IV cysts. In addition, the small number of solitary intrahepatic cysts are also included in this category. In 1973, Klotz[20] presented 4 patients and included an additional 5 patients previously reported in whom there were biliary cysts associated with some form of biliary atresia, and Kasai[21] in 1970, reported 8 more patients with this association. The histopathology of the cysts consists of a fibrotic wall which may or may not be lined with epithelium. An attempt was made in this review to correlate the presence or absence of an epithelial lining with congenital versus acquired types of cysts. No correlation could be found. When present, the epithelium is cylindrical or cuboidal and irregularly stained with bile pigments. The remainder of the cyst wall consists of dense, collagenous connective tissue with occasional elastic fibers and smooth muscle. Often an inflammatory reaction is present. The thickness of the wall has been reported from 2 mm to 10 mm.[14] The cysts are filled with bile, the character of which depends on the presence or absence of the gallbladder, and the degree of obstruction. Various sized cysts have been reported ranging from 1 cm and containing only a small amount of bile to cysts containing over 5000 cc of fluid.[14] The fluid may be sterile or may contain practically any combination of bacteria including staphylococci and streptococci, but with gram negative rods predominating. Seventeen cases of cystlithiasis have been reported;[16,21–27,148] two additional cases are R.J. and R.S. presented above.

Statistical Analysis of Cases

The incidence of biliary cysts can still be considered rare. During the 6-year period 1968 to 1974, only 4 new cases could be found at both the University of Michigan Hospital and St. Joseph Mercy Hospital in Ann Arbor. It is generally accepted that there is a predominance in the Japanese (over one-third of the cases are from Japanese literature). In an analysis of 820 cases, 81% of the patients were females. The age of patients at the time of diagnosis was quite variable (Table 2). Over one-fourth of the patients were less than one year of age (many were neonates), and over one-half were less than ten years of age. The fact that there are so many young patients is often used to support the congenital theories of etiology, however, it should be noted that 23% of patients seen are over 40 years of age. Whether this latter group has a congenital predisposition or their cysts were acquired secondary to some other disease of the biliary tree, is an area of great controversy.

The classical clinical presentation of biliary cysts is said to be a triad of right upper quadrant mass, abdominal pain and jaundice. Of 740 cases, only 38% presented with a classical triad. Jaundice was present at some time in 64%, a mass was found in 58%, and pain was part of the presenting symptomatology in 55% of cases (Table 3). The duration of the symptoms could be ascertained in 422 patients. It can be seen from Table 4 that most patients have symptomatology for a substantial amount of time prior to diagnosis. It is not at all unusual to elicit a history of many years of intermittent right upper quadrant pain and jaundice in the elderly patient with a biliary cyst.

In the 760 cases in which the type of cysts were mentioned, 86.7% were Type I, 3.1% Type II, 5.6% Type III, 2.6% Type IV and 2% were associated with biliary atresia (Table 5).

Etiology

The multiple theories of the etiology of biliary cysts have been described very well in Shallow's[14] and Saito's[19] reviews of the subject. The major controversy concerns congenital versus acquired origin of the cysts. Multiple theories concerning the mechanisms of formation of acquired cysts as well as mechanisms of formation of congenital cysts were presented in those reports. At the time of his publication, Shallow suggested that Yotsuyanagi's theory[10] was the most sound and accounted for the greatest number of cases. Other authors including Saito have since agreed.[15–17,19,20] Yotsuyanagi suggested that there is an inequality of proliferation of epithelial cells at the stage when the primitive biliary ducts are still

TABLE 3. *Presenting Symptoms (740 Cases).*

Jaundice	Mass	Pain	Triad
64%	58%	55%	38%

TABLE 4. *Duration of symptoms prior to diagnosis (422 Cases).*

< one wk	1-4 wks	1-5 mon	0.5-4 yrs	5-19 yrs	> 20 yrs
10%	9%	33%	26%	18%	4%

solid. If the cellular proliferation is more active at the proximal end than at the distal portion during the stage of epithelial occlusion, then at the time of canalization, the proximal portion will be abnormally dilated and the distal portion will be normal or somewhat stenotic. The Type IV lesions found in neonates obviously support the congenital cyst theory.

Most recently Babbitt, et al.[29] have proposed a new concept of etiology based on 7 cases in which they found a persistent anatomic aberration. In all 7 cases, the common duct inserted at right angles into the pancreatic duct at an abnormally long distance from the ampulla of Vater. This abnormal condition resulted in a loss of the normal sphincteric mechanism at the pancreaticobiliary junction. Babbitt and co-workers hypothesized that since the secretory pressure in the pancreas is greater than that in the liver, pancreatic juice would freely reflux into the common bile duct. They further support this by a high amylase content in the biliary cyst aspirate.

As mentioned above, 23% of cases present after the age of 20. Those who support the congenital theory will explain this fact by concluding that for some unknown reason the cyst or defect remained asymptomatic until that time. Kozloff et al.[30] however, have recently presented 5 cases of biliary cysts in adults which they believe were acquired rather than congenital. Some of the patients had previously negative common bile duct explorations only to have a cyst found at subsequent reoperation. This is certainly supportive of an acquired origin of the cyst, but obviously it does not negate the possibility of an undetectable congenital abnormality such as a point of localized weakness in the wall of the biliary duct. A similar situation is that of multiple biliary cysts. These would seemingly be congenital in origin, but there is no evidence to prove that they cannot be secondary to obstruction in a biliary system with multiple points of congenital weakness. Kato[156] has recently produced biliary cysts in puppies by scraping the mucosa of the bile ducts and following this with distal common bile duct ligation. The same effect was not reproducible in adult dogs.

It is generally accepted that biliary cysts may be congenital in origin, however, in view of cases such as Kozloff's and patient R.J. above which are beginning to accumulate, it would seem only reasonable to assume that in some cases the cysts may be acquired. Whether they are secondary to a congenital weakness has not yet been determined. Until further research is done in this area, the etiology will continue to be based on logically derived but unfortunately, unproven theories.

Diagnosis

It is the exception rather than the rule to make the diagnosis of biliary cysts preoperatively. In the earlier series it was actually a rarity to make the diagnosis preoperatively. In recent reported collected series by Alonso-Lej[16] and Lee,[17] however, the preoperative diagnosis was made in 35% and 27% respectively. More recently, Saito[19] reported a correct preoperative diagnosis in 80% of 39 cases. The importance of a correct preoperative diagnosis was shown to affect operative mortality in an early series by Tsardakas et al.[15] in which they showed a 56.6% mortality rate if the cyst was undiagnosed preoperatively versus a 30.5% mortality if it was diagnosed preoperatively. At the present, the overall operative mortality is about 4%.

There are multiple reasons why the diagnosis is usually missed, the most common one being that it is not usually included in the differential diagnosis.[16] Jaundice, right upper quadrant pain, and right upper quadrant mass are most common and the intermittent nature of these signs and symptoms, occasionally extending over a period of years, deserves emphasis.

Standard contrast roentgenography of the abdomen is not always sufficient to establish a diagnosis. Upper GI will usually show displacement of the antrum and duodenal bulb anteriorly, inferiorly and to the left. In Type III lesions, only a polypod structure may be seen intralumenally near the ampulla of Vater. Barium enema may show downward and sometimes anterior displacement of the hepatic flexure. Intravenous pyelography may show an inferiorly displaced right kidney, occasionally with a distorted collecting system. Although visualization of the gallbladder has been reported with oral cholecystography,[31] it usually does not visualize because patients with biliary cysts present in a jaundiced state in the majority of cases. The same reasoning holds for the frequent failure to visualize the bile ducts on intravenous cholangiography. Rose Bengal scans have been shown to be of benefit in the past but have not been used to a great extent.[21,32-35] Ultrasonography is very accurate in diagnosing the presence and location of a cyst, but cannot prove the biliary origin.[36] Success with total body opacification and the use of the rim sign to delineate the cyst has also been reported.[37]

In most cases prior to this decade, the diagnosis of biliary cyst was not made prior to operation. However, with the new technique of endoscopic retrograde cannulation and contrast injection of the common bile duct, the situation is changing. This procedure need not be the first

TABLE 5. *Classification of cysts by type (760 Cases).*

Type I	Type II	Type III	Type IV	Those associated with biliary atresia
86.7%	3.1%	5.6%	2.6%	2.0%

diagnostic procedure performed but is of utmost importance when there is failure to visualize the biliary tree on intravenous cholangiography. Retrograde injection is not always a benign procedure. About 50% of subjects will have a rise in serum amylase levels[155] and occasional cases of fatal pancreatitis have occurred.[154] Overdistention of the biliary tree with too large a bolus of Hypaque can precipitate gram negative sepsis since most of these patients have some element of bile stasis and infected bile. In Japan and some centers in the United States, it is current practice to inject antibiotics into the duct along with the Hypaque.[38] Current reports indicate a success rate for cannulation of the duct in excess of 80%.[153-155]

Complications

It is generally accepted that no treatment or medical treatment of biliary cysts are both almost uniformly fatal. In Tsardakas' report,[15] 29 of 30 patients treated medically died from the disease, and in a series reported by Attar,[152] 21 of 22 died, with one lost to followup, thus giving a 97% mortality rate for nonsurgical treatment of biliary cysts.

Traumatic spontaneous rupture of these cysts has been reported on many occasions.[15,21,24,41] Chen[42] recently reported 16 patients, three of whom presented with rupture and bile peritonitis. These cysts have also been reported to rupture during labor[150] and 23 cases have been reported to have ruptured during pregnancy.[24,30,40,44]

The presence of long standing, intermittent or partial obstruction leading to biliary cirrhosis has been recognized for a long time and is referred to in most reports. Kirwan[45] has recently reported 8 cases in children. Five of the children underwent liver biopsy and all 5 showed some degree of biliary cirrhosis. In addition to cirrhosis, severe bouts of cholangitis secondary to obstructive jaundice are common and are a leading cause of death in both unoperated and operated patients. Liver abscess has also been reported in association with biliary cysts.[46] Other complications include portal vein thrombosis with massive gastrointestinal hemorrhage, pancreatitis, and cancer.[46]

R.J., presented above, is the 24th reported case of cancer associated with biliary cysts,[19,23,130-148] thus establishing a 2.5% incidence.[47] Detailed analysis of these 24 cases is the subject of a separate report,[47] however, a few important differences between the biliary carcinomas associated with biliary cysts and other biliary carcinomas should be pointed out.

The incidence of biliary carcinoma has been reported from 0.0007% to 0.041% of all hospital admissions.[157] The 2.5% incidence of biliary carcinoma associated with biliary cysts is then clearly significant ($P < 0.001$). In a recent report by Longmire[158] concerning 63 patients with biliary carcinoma, 57% were males and 43% were females; the peak incidence was in the seventh decade.

Analysis of the 24 cases of biliary carcinoma associated with biliary cysts revealed a sex distribution of 33% males and 67% females. The average age at the time of diagnosis was 32 years with a range of 17 to 70 years. Only 4 patients were older than 36 years. The diagnosis of cancer was never made preoperatively and in 5 patients the diagnosis was made at autopsy. In only 6 patients were biliary calculi found. The most common cell type was adenocarcinoma, but cases of undifferentiated and squamous cell carcinoma were also reported. The most frequent site of origin was the posterior cyst wall, however, cases in which the tumor originated in both the proximal and/or distal biliary systems were also common. The average survival after diagnosis was only 8.5 months. The short survival was likely due to a delay in diagnosis accounted for by the fact that biliary obstruction did not occur as early as it would have in a normal biliary system. Once the obstruction did occur, the symptoms were not unlike the patient's previous symptoms which were atrributed to biliary cystic disease.

Treatment

The best operation for biliary cysts is still controversial. In this country, RYCCJ is presently being advocated for Type I cysts whereas in other countries excision is in vogue. Trout and Longmire,[48] Duckett,[49] and O'Neill[50] have presented papers in this country which have the longest followup periods. Only one case of excision is included in these studies.[48] This patient died 13 years after excision due to unrelated disease. Twenty-four of these patients collected by Trout and Longmire had undergone RYCCJ. Eleven developed morbidity and 5 required reoperation; none died. Forty-eight patients underwent CCD with 39 having significant morbidity and 22 requiring reoperation; two died. Only 9 cases of choledochocystjejunostomy (CCJ) were performed. Five had significant morbidity and five required reoperation. None of the patients undergoing CCJ died. Duckett presented 14 children. Twelve had CCD with no morbidity, or mortality. Two underwent RYCCJ and one of these died. O'Neill presented 11 patients. Ten underwent CCD. Six had significant morbidity, four required reoperation,

TABLE 6. *Results of operative treatment (235 Cases, 282 Procedures).*

Operation	# Of cases	Morbidity	Re-operation	Mortality
Excision	83	7 (8%)	0	6 (7%)
RYCCJ	53	18 (34%)	7 (13%)	9 (17%)
CCJ	12	6 (50%)	5 (42%)	1 (3%)
CCD	93	55 (58%)	35 (38%)	6 (5%)

and one died. One patient underwent RYCCJ and did well. The reports of Trout and Longmire, Duckett, and O'Neill are included in the analysis below. Other operations such as sphincteroplasty,[51] choledochocystgastrostomy[18] and external drainage[17] have been performed but are generally condemned. In addition, not enough of these latter procedures have been performed to make a statistical analysis significant. Tsardakas[15] originally showed a 65% mortality with external drainage alone as therapy. External drainage is still a valid initial procedure in a poor risk patient, but should be followed with a definitive procedure when the condition of the patient permits. Little controversy exists over the treatment of Type II and Type III lesions. Excision of a Type II cyst with ligation of the base of the stalk of the diverticulum is usually easily performed. Transduodenal resection of choledochoceles with choledochoduodenostomy is the procedure of choice for Type III lesions.[48] Type II and III cysts are admittedly rare lesions, however, and good followup data are not available. In some cases of multiple biliary cysts and those associated with atresia, no procedure can be recommended. The operation must depend on the individual anatomy.

The primary controversy then involves Type I cysts. The accepted operations under consideration are excision, RYCCJ, CCJ, and CCD. Excision is not often performed in this country primarily because of the reportedly high mortality rate. This mortality was reported in 1959 by Alonso-Lej to be 15%.[16] Lee has shown a steady decrease in the overall operative mortality (all procedures) from 1943 (51%) to 1969 (5.2%).[17] This can no doubt be attributed to new methods of diagnosis and new expertise which has evolved in the operative and perioperative care. For this reason, only cases reported in recent series with good followup are included in the following analysis.

A statistical analysis of 235 cases reported from 1968 to 1972 with an average followup of 5.2 years is shown in Table 6.[18–21,26,48–50,52–56] Only Type I cysts were included. Mortality rates include operative deaths plus late deaths which were related to the biliary disease or to the operation performed. Thus, they are generally higher than recent reports showing only operative mortality.[20] Morbidity in this report consisted of anyone or of any combination of recurrent pain, jaundice, stricture formation or obvious cholangitis. The mortality rates show no significant difference between RYCCJ and excision, 17% and 7% respectively ($P < 0.1$). A morbidity of 34% for RYCCJ versus 8% for excision is more impressive, however, ($P < 0.01$). Also, no patient undergoing excision required reoperation whereas 13% with RYCCJ required reoperation ($P < 0.01$). The morbidity (50%) and reoperation rate (42%) for CCJ does not seem to make this a desirable operation although the number of cases presented is low. CCD had only a 6% mortality rate, but a 58% morbidity rate and a 38% reoperation rate would tend to make this a less effective procedure. The difference between mortality in CCD versus excision is not significant. The large mortality recorded here for RYCCJ is obviously due to the definition of mortality in this report. In Klotz's study, 144 cases reported after 1968,[20] he presented operative mortalities for CCD, RYCCJ plus CCJ, and excision as 2%, 5% and 4% respectively. There is clearly a significantly higher morbidity for internal drainage procedure than with excision. This is probably secondary to reflux of small bowel contents into the cysts with stasis[49] or to stricture formation.[48] There is less cholangitis with RYCCJ than CCD as would be expected. No instances of peptic ulceration have been reported in cases of biliary cysts treated with RYCCJ.

Another factor to be considered in making the choice of operation is the 2.5% incidence of biliary cancer which is associated with biliary cysts. In a separate analysis,[47] 50% of the reported cases of carcinoma in association with biliary cysts occurred a mean of 4 years after an initial internal drainage procedure.

These findings indicate that the procedure of choice foi Type I biliary cysts should be excision when the anatomy, the condition of the patient, and the skill of the surgeon permit. The technique has been nicely described by Saito[19] (in English). If excision is to be performed, it is probably advisable that cholangiography and pancreatography be carried out either intraoperatively or preoperatively because cases of the pancreatic duct draining into the biliary cyst have been reported.[28,57] The usual reconstruction following excision is Roux-en-Y hepaticojejunostomy (RYHJ), however, Scarli,[54] Cahlin,[26] and Longmire[58] each reported a case in which sufficient common hepatic duct and common bile duct remnants remained after excision so that a primary anastomosis of common hepatic duct to common bile duct could be performed. RYCCJ is less successful than excision, but is a good alternative operation. CCD is the least successful of the three procedures. Concomitant cholecystectomy and appendectomy have been recommended.[18,21,48] As stated above, most of the cases undergoing excisional therapy are from Japan. Considering the data which are now available, it would seem warranted that excisional therapy be more widely used in this country. Saito[19] has reported no operative mortality in his last 20 patients treated by excision.

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Massive Ringer's Lactate Infusion:

Comparison With Dextrose 5% and Whole Blood

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The objectives of this study were to compare in dogs the effects of massive infusion of Ringer's lactate, 5% dextrose in water, and whole blood. Special interest centered upon lung function, central venous pressure, and dilutional effects upon the blood components. Three groups of 5 healthy dogs each received respectively Ringer's lactate, 5% dextrose, or whole blood over 60 minutes in the amount of 135 ml/kg. Arterial blood gases and pH, right atrial and systemic arterial pressures, hemoglobin and hematocrit values, and plasma sodium, chloride, potassium and protein levels were determined. Coagulograms and serum osmolality were examined in the early experiments. The purpose of the whole blood infusion was primarily to serve for comparison in the study of dilutional effects upon blood components. There was no statistically significant change in the arterial blood gas values or pH following Ringer's lactate infusion. The infusion of 5% dextrose in water produced moderate decline in arterial P_{CO_2} and a temporary, slight fall in blood pH. Ringer's lactate infusion produced a prompt and statistically significant rise in central venous pressure. The infusion of 5% dextrose was followed by a late moderate decline in arterial blood pressure, possibly due to marked dilution of plasma sodium, chloride and potassium. It is concluded that massive Ringer's lactate infusion is capable of increasing right atrial pressue and presumably cardiac output. In healthy dogs, lung function was not impaired sufficiently to alter arterial blood gas values. However, where other previous or concomitant factors have diminished pulmonary reserve, fluid overload may impose a serious additional burden upon cardiopulmonary function.

THE USE OF RINGER'S LACTATE for fluid replacement in patients has become widespread and indeed almost universal. This resulted from the rationale that a balanced electrolyte solution was superior to isotonic sodium chloride which contains a physiological excess of chloride ions. In general the infusion of Ringer's lactate has been effective not only in emergency resuscitation prior to the availability of whole blood for transfusion, but also in reducing the need for single transfusions and in routine fluid therapy. However, in many instances the amount of Ringer's lactate infused has appeared to be excessive, as for example during resuscitation of the traumatized patient and especially during operation when the blood loss may have been nominal. Before the recent interest in Ringer's lactate it was normal saline that was over infused.[1] Relatively huge volumes of electrolyte solution may be harmful even while being administered. Moreover, should the patient subsequently become oliguric, he begins the post-stress period with a serious fluid overload (Fig. 1). This excessive hydration may contribute to the numerous factors which can contribute to the development of acute respiratory insufficiency (Fig. 2).

The objectives of the present series of investigations were several. First, the effect of a large and rapid infusion of Ringer's lactate upon lung function was to be compared with the effect of 5% dextrose in water. Second, the effectiveness of the Ringer's lactate in elevating central venous pressure was also to be compared with that of 5% dextrose in water. The ability of colloid solutions such as plasma, dextran or whole blood to raise central venous pressure was considered well established. Third,

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the dilutional effects upon plasma protein and electrolytes, and upon blood hemoglobin and hematocrit levels were to be determined. Here whole blood infusions were employed for comparison with the effects of the two non-colloid solutions.

Methods

Three groups of five dogs each were used. The animals had been carefully examined and treated for parasites and other diseases, and they were judged by the veterinarian to be in good health. Each weighed approximately 17 kilograms, and each received 135 mg/kg of the test fluid intravenously over a 60 minute period.

The test animal received repeated small doses of Surital (thiomylal sodium) intravenously as required to preserve mild sedation and analgesia. Prior to the infusion a catheter was passed through the external jugular vein into the right atrium for central venous pressure monitoring, and a catheter was inserted into a femoral artery for measurement of "mean" pressure and for arterial blood samples. Mean arterial pressure was that recorded when the oscillations of the recording arm had been damped to abolish the systolic and diastolic fluctuations. The test fluid was infused through a femoral vein and a forearm vein. Originally it had been planned to infuse the Ringer's lactate, 5% dextrose or whole blood serially into each animal at two week intervals with the blood infused last, but this proved during the pilot experiments to be a less than optimal procedure. Therefore, 15 dogs were ultimately employed for the definitive experiments, using the counter-balanced technique to reduce possible statistical error caused by increasing facility with the experimental methods and techniques. That is, one dog received Ringer's lactate, the next whole blood, and the third 5% dextrose in water, in rotation. Monitored during the 60 minute infusion period and for several hours thereafter were arterial pressure, right atrial pressure, blood hematocrit and hemoglobin, plasma protein, arterial blood gas values and pH, serum osmolality in some animals, urine output, and plasma sodium, potassium and chloride levels. Blood coagulograms were also determined in the early experiments, but when little change was found these expensive measurements were discontinued. Pulmonary wedge pressure was measured in some but not all animals. Most dogs survived the experiment. Autopsy was performed when a death occurred. By and large, the most conspicuous post-mortem findings were ascites and, to a lesser degree, pleural effusion. Gross clinical evidence of pulmo-

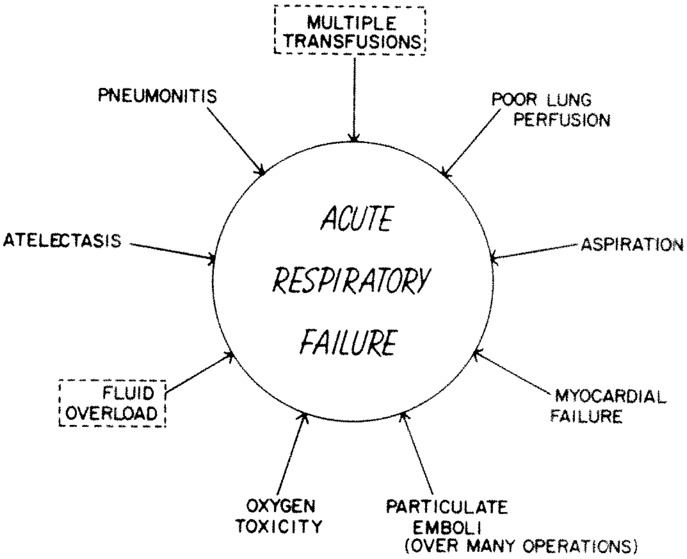

FIG. 2. Possible contributing factors in respiratory distress exhibited by patient M.S. (Fig. 1).

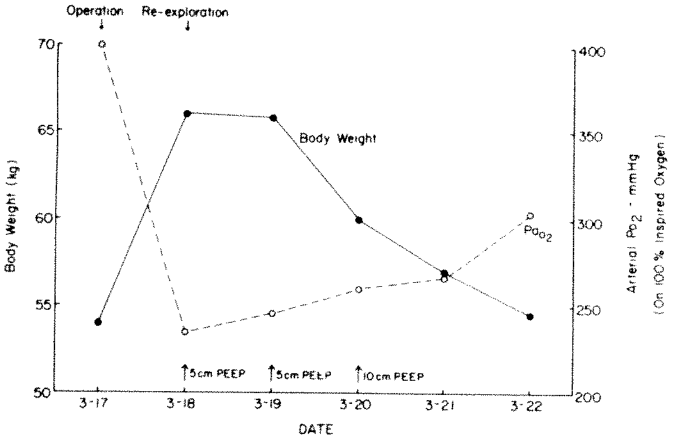

FIG. 1. *Illustrative Case*. M. S., A 65-year-old woman, underwent extensive intra-abdominal aortoiliac surgery, which represented her twelfth vascular procedure over a period of 8 years. She gained 11 kilograms in the postoperative period, during which time she exhibited clinically obvious cardiopulmonary embarrassment. There was an inverse correlation between fluid retention (weight gain) and the P_{aO_2}.

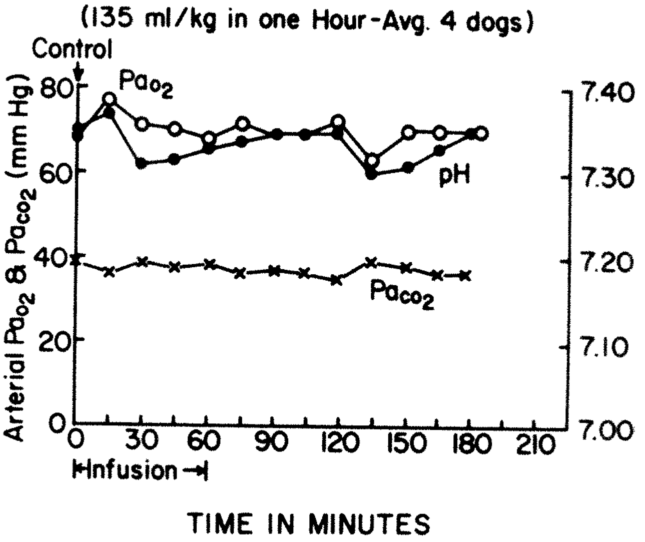

FIG. 3. Massive Ringer's lactate infusion caused no statistically significant change in arterial P_{O_2}, P_{CO_2}, or pH.

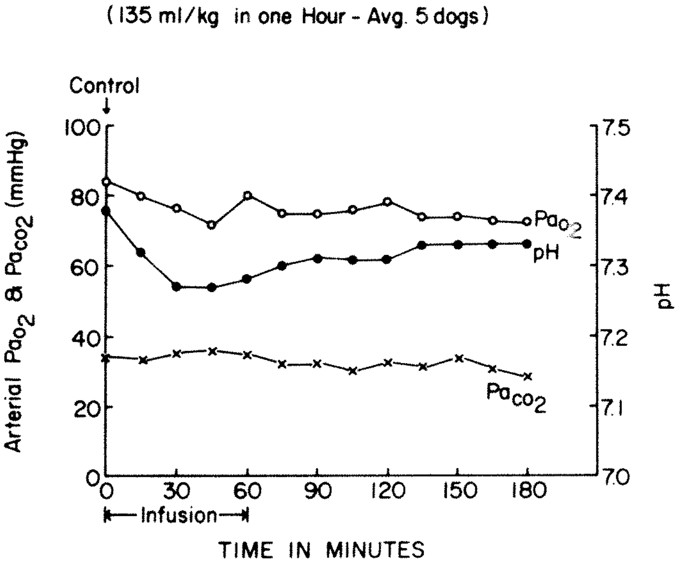

FIG. 4. Whole blood infusion effected no statistically significant change in Pa_{O_2}, Pa_{CO_2} and pH.

nary edema was noted occasionally in both survivors and non-survivors.

Results

The data for the dogs receiving Ringer's lactate 135 mg/kg, those receiving 5% dextrose in water 135 ml/kg and those receiving whole blood 135 ml/kg are presented in Figs. 3-11. The data for one dog in the Ringer's lactate group were incomplete, and thus the pertinent graphs reflect the averaged values in 4 dogs. The findings in the 3 groups of dogs will be presented under arterial blood gases and pH, blood pressure, and the concentrations of blood components. However, elevations in blood hematocrit and hemoglobin levels represented the only statistically significant changes in measured components produced by whole blood infusion.

Arterial Blood Gas Values and pH

The arterial blood gas values and pH for the dogs that received Ringer's lactate, blood, and dextrose 5% are presented in Figs. 3-5. There was no statistically significant change in the P_{O_2} of either group. There was an observable but non-significant decline in the pH in the dextrose group during the infusion, with rapid recovery thereafter; the P_{CO_2} declined slowly but steadily in this group over the 3 hour period of observation. In the Ringer's lactate group there was a mild but non-significant decline in the arterial blood pH during the infusion but essentially no change in the P_{CO_2}.

Arterial and Central Venous Pressure

Arterial Pressure. The Ringer's lactate (Fig. 6) and whole blood (Fig. 7) infusions produced no significant change in mean arterial blood pressure. However, it should be noted that most animals were mildly hypertensive during the pre-infusion control period, due to the excitement and mild stress imposed by placing them on the operating table. In contrast, the infusion of the large amount of 5% dextrose in water (135 ml/kg) resulted in a statistically significant decline in arterial blood pressure (Fig. 8), which accompanied a decline in serum electrolyte values.

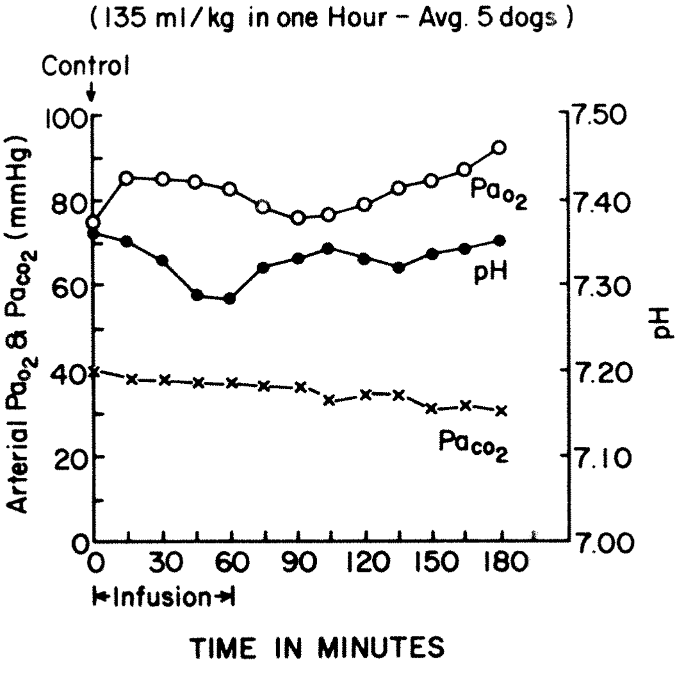

FIG. 5. Massive 5% dextrose infusion produced no statistically significant change in arterial P_{O_2}, P_{CO_2}, or pH.

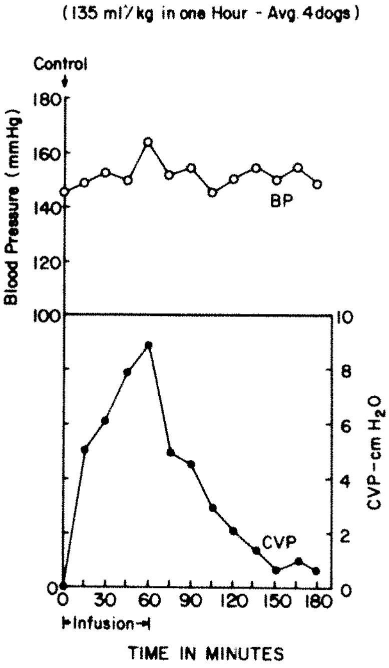

FIG. 6. Ringer's lactate infusion promptly and significantly increased the central venous pressure, without significant change in blood pressure.

Central Venous Pressure (CVP). The changes in central venous pressure following Ringer's lactate infusion, as compared with whole blood or dextrose infusion, are presented in Figs. 6-8. The Ringer's lactate significantly increased the central venous pressure ($P<0.05$) by the time 25% of the fluid was infused, and the pressure remained significantly higher until 30 minutes after completion of the infusion. At no time was there a significant difference during or after dextrose infusion, although the CVP increased considerably in two animals at the start of the dextrose infusion and remained elevated in one.

A rather rapid decline in the right atrial pressure occurred after the infusion was discontinued, though moderate elevation persisted for another 30 minutes or so.

Concentration of Blood Components

Plasma Electrolytes. The data for sodium, chloride, potassium, and protein in the Ringer's lactate, whole blood and 5% dextrose group are presented in Figs. 9-11. As expected, the Ringer's lactate animals exhibited no significant change in the plasma sodium and chloride levels. There was a mild but statistically insignificant decline in the plasma potassium level. All electrolyte values declined significantly during the 60 minute dextrose infusion, and some effect persisted for hours (Fig. 11).

Plasma Proteins. The plasma protein levels declined significantly in both the Ringer's lactate ($P<0.05$) and the 5% dextrose ($P<0.05$) groups during infusion, with significant effect persisting for the duration of the experiment (Figs. 9 and 11). There was no significant change in the plasma protein levels of the dogs that received whole blood.

Hemoglobin and Hematocrit Levels. The hemoglobin and hematocrit levels followed expected patterns.[5] In the Ringer's lactate and 5% dextrose groups there was marked hemodilution, with significant decreases of hematocrits in both groups. In the whole blood group there was significant hemoconcentration, with marked elevations in hemoglobin and hematocrit levels. The hematocrit had fallen significantly ($P<0.005$) in the Ring-

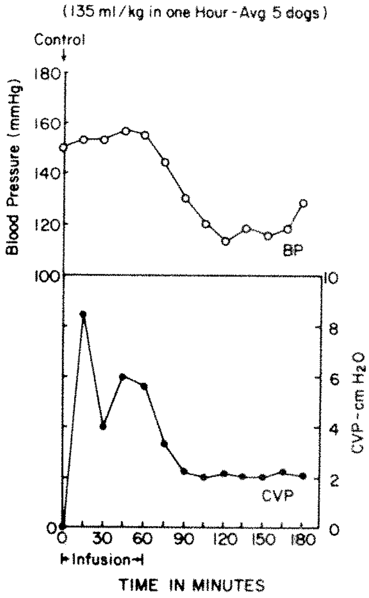

FIG. 8. Dextrose 5% infusion produced an average increase in central venous pressure, but this change was not statistically significant, nor was the moderate decline in arterial blood pressure.

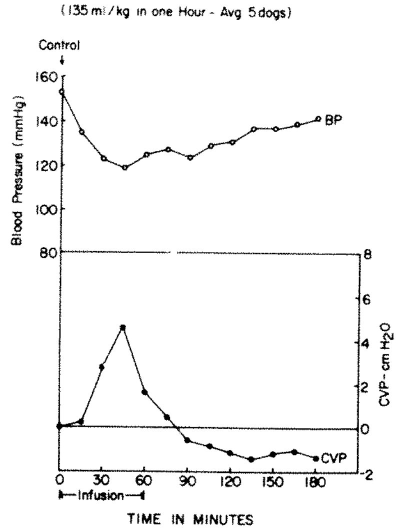

FIG. 7. Whole blood infusion caused a statistically significant rise in central venous pressure.

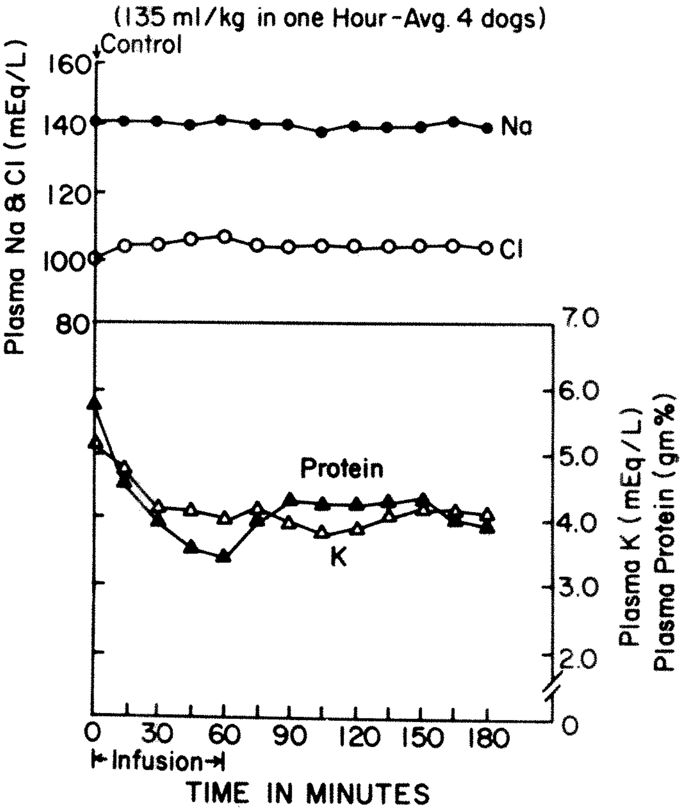

FIG. 9. Ringer's lactate infusion produced no significant change in plasma Na, K, and Cl levels. The serum protein level was significantly decreased.

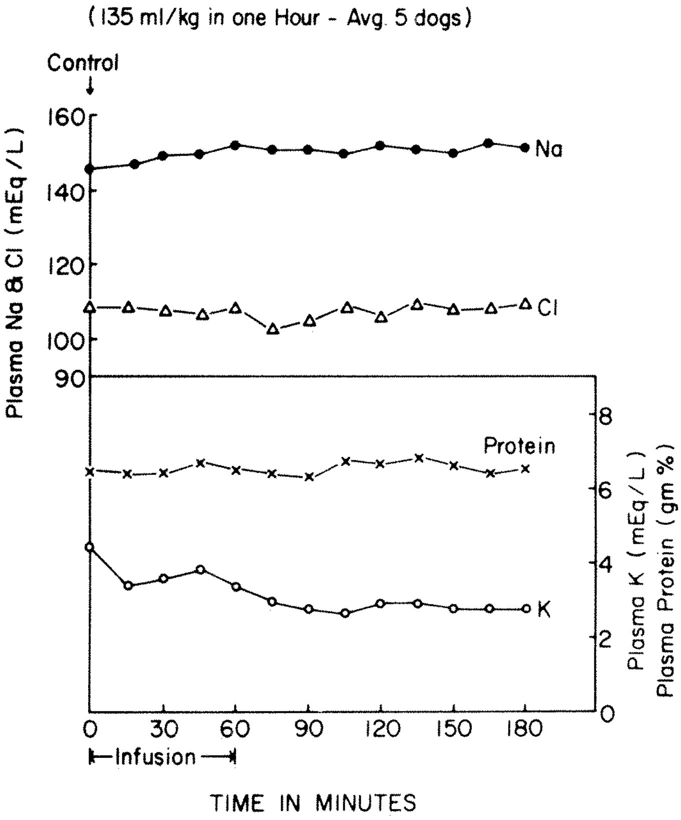

FIG. 10. Whole blood infusion produced no statistically significant change in plasma Na, Cl, K, or protein.

er's lactate group when only one-half the fluid had been infused, and in the dextrose group (P<0.01) when one-fourth the fluid had been infused. Thirty minutes after infusion of either Ringer's lactate or dextrose the hematocrit began to rise and was normal at two hours.

Serum Osmolality Values. The serum osmolality changes were not measured routinely, but where determined there was relatively little change in the Ringer's lactate and whole blood groups but a significant reduction in the serum osmolality in the 5% dextrose group.

Discussion

Effect of Massive Fluid Administration on Lung Function. A primary objective of these studies was that of assessing the effect of massive Ringer's lactate infusion upon lung function, as reflected in arterial blood gas values and pH. It was anticipated that a significant impairment of respiration might be documented. However, such was not the case: the relatively huge infusions of Ringer's lactate and of 5% dextrose in water had little effect upon the arterial blood gas values in these healthy dogs, attesting the substantial pulmonary functional reserve which normally exists. Thus, while an unexpected finding, our data indicated that in the absence of pulmonary disease large amounts of non-colloid solution can be rather well tolerated. However, moderation is always desirable since pulmonary dysfunction due to other causes may develop in the surgical patient at any time. Furthermore, it is to be recalled that both ascites and pleural effusion were noted in some of the dogs that came to autopsy, and clinical experience is in accord with such findings.

Effect of Massive Fluid Administration on Central Venous Pressure and on Mean Systemic Arterial Blood Pressure. A major secondary objective of these stuides was that of quantitating the effect of the infusion of a massive volume of non-colloid solution upon central venous pressure. The influence upon systemic arterial pressure was also to be recorded. Moss et al.[4] demonstrated, as had others,[3] that electrolyte solutions increase cardiac output when infused as shock therapy. The capacity of colloid solutions to elevate control venous pressure was considered established.

The infusion of Ringer's lactate produced a prompt rise in central venous pressure, from approximately zero to an average of between 8 and 10 cm H_2O, a statistically significant change. Dextrose 5% infusion produced a rise in CVP in some animals, but this result was not a consis-

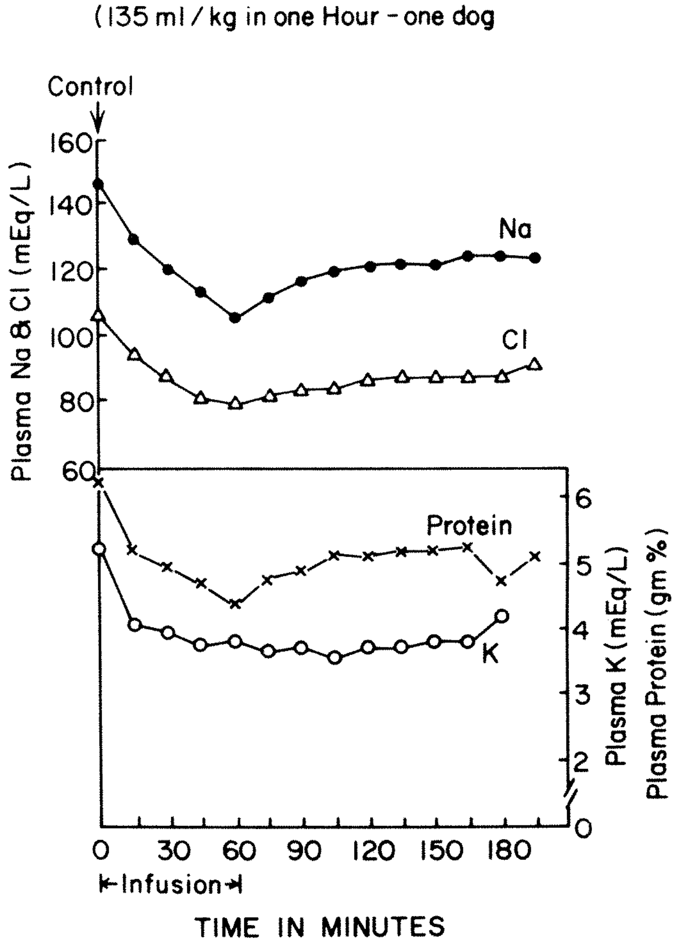

FIG. 11. Dextrose 5% infusion caused a significant decline in serum Na, K, Cl, and protein levels.

tent one and was not statistically significant. Clearly, Ringer's lactate infusion is useful in the emergency situation and even dextrose 5% is better than nothing. However, the massive infusion of 5% dextrose in water was associated with a modest late decline in systemic arterial blood pressure, possibly due to dilution of the extracellular sodium, chloride and potassium. Inasmuch as there was little electrolyte dilution and no late decline in systemic arterial blood pressure following massive Ringer's lactate infusion, the decline in plasma protein concentration exhibited by both groups would not appear to have been responsible for the blood pressure decline in the 5% dextrose group. Actually, the average decline in the 5% dextrose group was only about 30 mmHg, though this was to be compared with no decline in the Ringer's lactate group.

Pulmonary wedge pressure was not measured in enough animals to permit statistically valid conclusions. However, in other studies we found considerable disparity between the effect of infused fluid upon right atrial pressure as compared with left atrial pressure.[2]

Effect of Massive Fluid Administration on Plasma Electrolyte, Protein, Hemoglobin, and Hematocrit Levels. The Ringer's lactate infusion resulted in little change in the plasma electrolytes, but the protein, hemoglobin and hematocrit levels declined. Similar changes in hematocrit levels were recorded by Takaori and Safar.[5] In contrast, all measured blood and plasma components were diluted by the massive 5% dextrose infusion. The plasma sodium level fell from a control value of 145 mEq to 115 mEq/L at the end of the 60 minute infusion. Such a severe dilution in the plasma sodium level could predispose to a state of water intoxication. Incidentally, the sharp fall in the plasma sodium and chloride levels which followed the dextrose infusion was accompanied by the expected sharp fall in serum osmolality. The decline in plasma protein levels which followed the infusion of either Ringer's lactate or 5% dextrose in water could promote an increase in extravascular lung water.

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Joining Gut Ends of Unequal Diameter

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A simple, safe and precise method for joining ends of unequal diameter is presented. Very little septum is created by either anterior or posterior rows. The figure-eight seems to crush the septum almost flat on the posterior row and the Halsted's create an absolutely minimal septum anteriorly where they are correctly placed. The posterior row uses two layers of submucosa and the anterior one, four layers, and no reliance is placed on the serosa-muscularis layer. This technique is thought to have distinct advantages relative to strength, safety, and minimal septum formation.

CREATING A SATISFACTORY ANASTOMOSIS between gut ends of unequal diameter is often necessary. Several techniques have been developed, probably the most ingenious was by Dr. Truman Blocker, Jr.[1] This was a plastic procedure, with somewhat complicated steps which discourage general surgeons from adopting it, although basically it is a sound technique. Today, most surgeons equalize the end diameters by: 1) cutting the smaller end at a sharp angle from mesenteric to antimesenteric border in a distal-proximal direction, or 2) the use of the Cheatle incision, which we prefer. We believe the first method does not enlarge the resulting lumen nearly as much as is commonly believed, and hence is not as efficient or safe as the second method.

Method

Four traction sutures are placed (Fig. 1), stretching each lumen to its full diameter, with each mesenteric angle in the center. The ends are approximated and a single parallel mattress suture is placed very accurately adjoining the mesenteric angles of the two ends. This is a most important spot for perfect closure as leakage is most apt to occur here.

Figure 2 shows the outline of the proposed Cheatle incision which is not made at this time. The dotted line parallel to the long axis indicates the length of the Cheatle incision; the other two indicate the rounding off of corners.

Parallel mattress sutures (Fig. 3) unite ends to full extent of the diameter of the small end. Now the Cheatle incision is made, and the corners are rounded off.

The original traction sutures on the small end are removed (Fig. 4) and replaced so that the two lumens are now of equal diameter, and the rounding off of the corners of the Cheatle incision produces a fairly straight line. Now the posterior row of mattress sutures is completed out to each end, and a row of figure-eights completes the posterior row. At this point, a Connell suture at each end starts the inversion of the anterior row, and after tying these Connell sutures, they are used as the sole traction sutures, the others being removed at the same time.

The Connell's on each end are now used as the traction sutures, and a row of Halsted's closes the anterior row (Fig. 5). All the Halsted sutures are placed before any are tied. This produces minimum of a septum.

After tying the Halsted sutures, Lembert sutures are placed between them to insure a watertight closure (Fig. 6).

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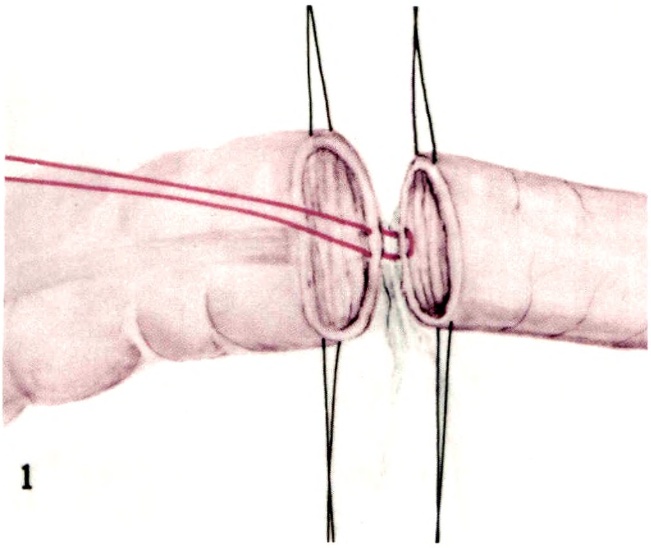
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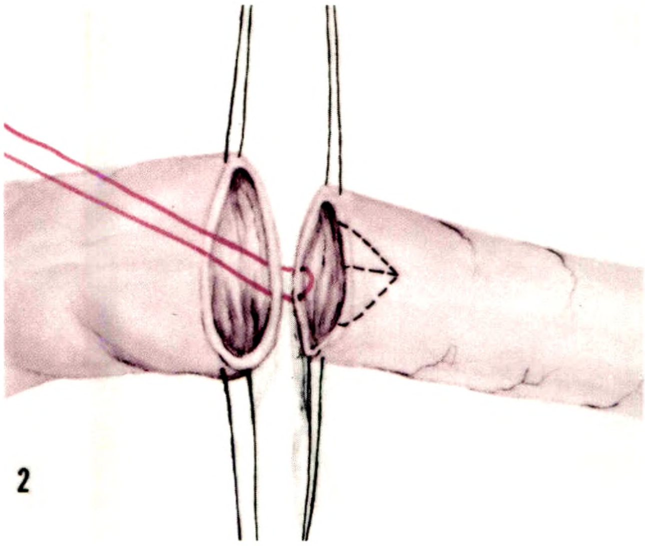
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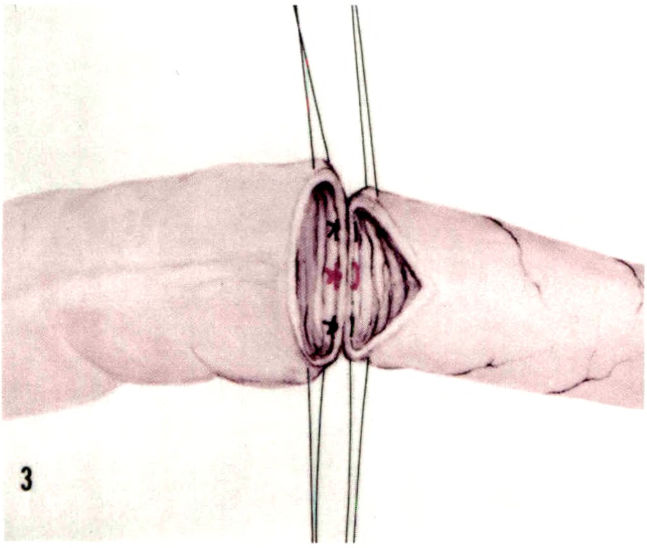
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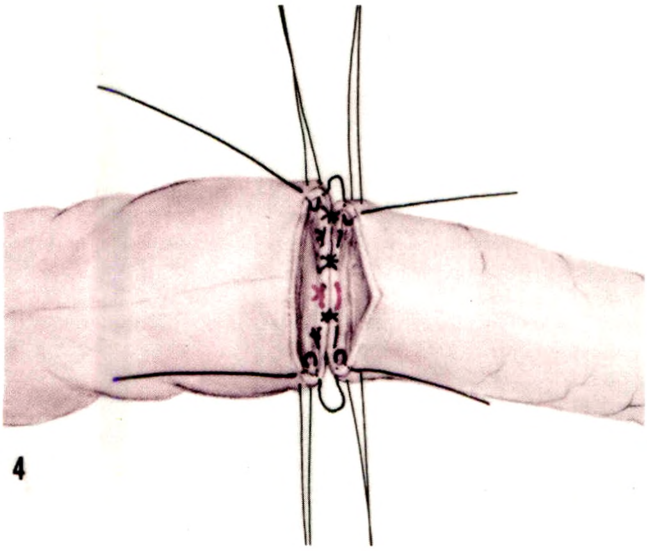
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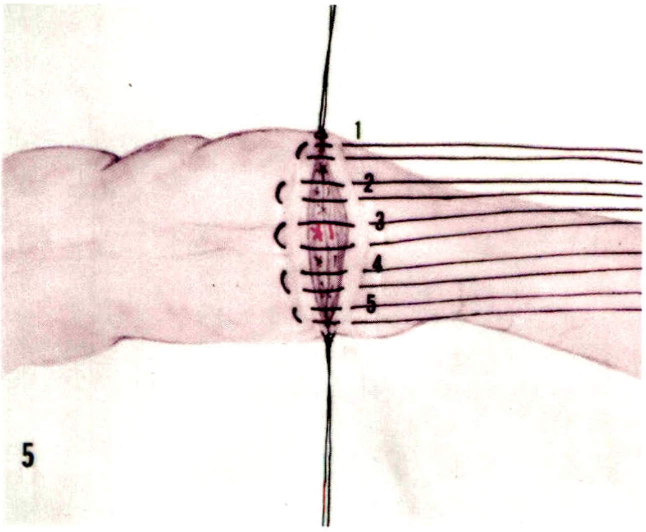

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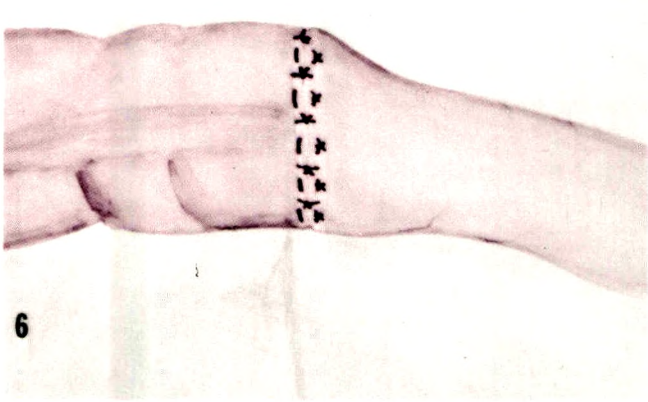
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The Pathophysiology of Smoke Inhalation Injury

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The consequences of near-lethal smoke inhalation in dogs were studied for a 72-hour period following injury. Progressive hypoxemia and decrease in compliance developed. Severe respiratory distress and frank pulmonary edema were not encountered. Respiratory insufficiency was related more to alterations in ventilation perfusion ratios than to alveolar destruction. These data were related to clinical observations made by others. No deterioration of lung function was seen with crystalloid overload imposed upon smoke inhalation. The presence of bacterial infection in dogs surviving beyond 24 hours appears pathogenically significant.

CARBON MONOXIDE and smoke poisoning are the major causes of early death resulting from fire.[19] Although many people die within minutes of the fire, some suffering the effects of smoke inhalation reach the hospital. Not infrequently, smoke inhalation is the only injury sustained by the victim. If the patient has sustained cutaneous thermal injury, the respiratory state is complicated by severe hypovolemic shock, massive tissue destruction, large volume fluid therapy, and infection. Compared to the magnitude of the problem of thermal injury and concomitant smoke inhalation in the United States,[12,19] relatively little is known about the pathophysiology of uncomplicated smoke inhalation. To date, it is not possible to separate the respiratory effects of inhalation injury from the ventilatory effects of shock, massive fluid therapy, burn wound toxins, and sepsis.

Laboratory studies have failed: 1) to establish the basic mechanisms responsible for respiratory failure from smoke inhalation; 2) to divorce the effects of thermal injury entirely from inhalation injury; 3) to establish a time-course of pulmonary function following injury; 4) to separate upper airway injury from lung injury; and 5) to establish the role of bacterial infection in the development of pulmonary failure following smoke inhalation.

Most studies employ tracheal intubation to mimic the clinical picture of smoke inhalation through an intact respiratory tract. Although this laboratory technique may make the experimental injury numerically standard, it does not allow for the wide variation in lung injury observed clinically.

From laboratory and clinical experience, Stone and co-workers[13,17] have staged inhalation injury into three temporal phases: 1) respiratory insufficiency occurring in the 24-36 hours after injury, 2) pulmonary edema occurring after 8 hours, and 3) bacterial pneumonia as a late stage. A laboratory model was sought which would simulate such a picture. The model devised would have to allow smoke inhalation through an intact airway to the point of near asphyxiation, sequential measurement of cardiovascular and pulmonary function, temporal evaluation of lung disease, and be useful for measurement of pulmonary effects of simultaneous smoke inhalation and other potential pulmonary insults, such as crystalloid infusion and aspiration of bacteria.

Based on the study by Zikria and colleagues,[18] such a model was established using wood smoke and the dog. It was found that: 1) pulmonary function deteriorated for

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4-24 hours following injury, but that treatment-resistant insufficiency rarely developed in this time period; 2) pulmonary edema was an inconsistent finding; 3) crystalloid "overload" had no effect upon the injury; 4) cardiovascular dysfunction was as profound as respiratory dysfunction; and 5) bacterial pneumonia was the most important limiting factor to survival.

Methods

Mongrel dogs weighing between 12 and 31 kg were given intravenous pentobarbital (30 mg/kg), and the trachea was intubated. Systemic arterial catheterization was performed through the femoral artery for measurement of mean arterial pressure (MAP) and arterial blood gases. A Swan-Ganz catheter was passed through a jugular vein into the pulmonary artery for determination of pulmonary artery pressure (PAP), wedge pressure (PWP), and retrieval of mixed venous blood. The endotracheal tube was then connected to a Collins spirometer for spirometric measurements (Tables 1 and 2). After initial variables were obtained, the endotracheal tube was removed, and the dogs were allowed to inhale wood smoke spontaneously from a specially designed apparatus.

This apparatus enclosed only the dog's head. A wood fire was ignited in a remote combustion chamber, and smoke was conducted into the chamber containing the dog's head. With the temperature of the chamber being monitored (47.3 ± 4.9 C), the dogs inhaled smoke for 5½-6 minutes. An 8-minute period of smoke inhalation was uniformly fatal. The dogs were removed from the chamber if bradypnea or apnea occurred. Most of the animals required immediate mechanical respiratory assistance to prevent death. Arterial blood gases obtained in the chamber were P_{O_2} 36.7 ± 11.0, P_{CO_2} 75.4 ± 5.1 and pH 7.137 ± .026.

At the end of the period of smoke inhalation, the dogs were again intubated and immediately placed on 100% oxygen delivered by the Collins spirometer. After 30 minutes the variables described in Tables 1 and 2 were determined. Percentage of water in the lung was obtained by taking small segments of the various lobes, weighing and drying to constant weight (3 days at 150 C). Then:

$$\%\ H_2O = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100$$

Oxygen consumption ($\dot{V}O_2$) was determined after a 10-15 minute stabilization period of ventilation with 100% oxygen.

After the 30-minute measurements were taken, the animals were disconnected from the spirometer and allowed to breathe room air spontaneously until the next series of measurements. Determinations were obtained at 2, 4, 24 and 72 hours after injury.

TABLE 1. *Methods of Determination*

Variable	Method of Measurement
Blood gases (P_{O_2}, P_{CO_2}, pH)	IL blood gas analyzer
$\dot{V}O_2$ (oxygen consumption)	Collins' spirometer (5 minutes)
Tidal volume	Collins' spirometer
Respiratory rate	Collins' spirometer
Expired CO_2	Beckman medical gas analyzer
Hemoglobin	Cyanmethemoglobin method
Vascular pressures	Beckman dynograph and Statham strain gauges
Compliance[5]	Harvard respirator (5 breaths)
Lung weight	Weighing
Lung per cent water	See text

Fourteen dogs were sacrificed at 4 hours for determination of weights, per cent of water and histologic examination of the lungs. Twelve dogs were sacrificed at 24 hours for similar data (one dog died on induction of anesthesia at 24 hours). Five dogs were scheduled to survive for 72 hours; however, two died between 48 and 72 hours. The latter seventeen dogs were extubated after 4 hours. Repeat anesthesia was necessary for the 24- and 72-hour measurements with recannulation of vessels and re-insertion of endotracheal tubes. In the event of death, anatomic data were recovered as soon as possible. Lung cultures were made from all the dying dogs. In 8 dogs, a crystalloid load of 10 mEq Na/kg (74.1 cc/kg) as Ringer's lactate was given in the 4 hours following smoke inhalation. Physiologic and anatomic variables were compared with the dogs sacrificed at 4 hours.

Histologic examination was made of segments of several lobes from all dogs. The tissue was fixed in 10% formalin, inbedded in parafin and stained with hematoxylin and eosin.

Results

Despite smoke inhalation to the point of near asphyxiation, no dog died before 4 hours, one dog of 12 died on induction of anesthesia at 24 hours and two of 5 died between 48 and 72 hours. The two dying late had evidence of bacterial pneumonia. There was a significant increase in lung weight at 4 hours as well as some increase in lung water (Fig. 1). The changes in lung weight

TABLE 2. *Calculated Variables*

Minute volume	Respiratory rate x tidal volume
Vd/Vt[3]	$\dfrac{\text{Expired } P_{CO_2} - \text{arterial } P_{CO_2}}{\text{arterial } P_{CO_2}}$
Cardiac output	Fick Principle
Blood O_2 content	([Hgb] x 1.34 x % O_2 Sat.) + .0031 P_{O_2}
Alveolar—arterial P_{O_2} gradient ($\Delta A - a\ P_{O_2}$)	Alveolar P_{O_2}—arterial P_{O_2}
Alveolar P_{O_2}	(Barometric pressure—47)—art. P_{CO_2}
Vascular resistance	$\dfrac{\text{Arterial pressure} - \text{Vein pressure}}{\text{Cardiac output}}$

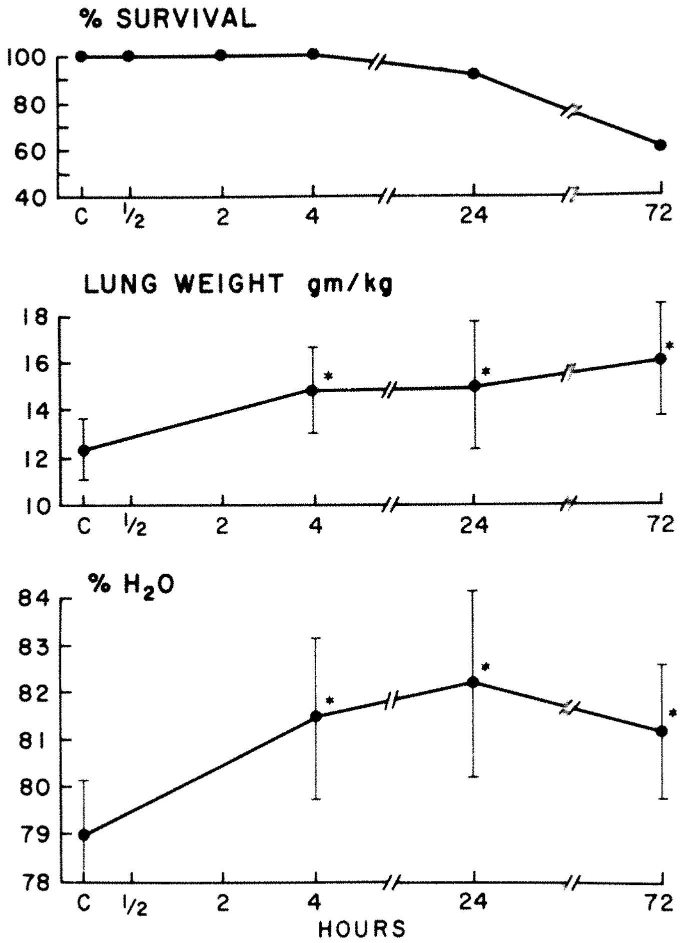

FIG. 1. (Top) No dog died within the first 4 hours after smoke inhalation. The only dog dying at 24 hours did so with the induction of anesthesia. The dogs dying at 72 hours died from pneumonia. (Center) Lung weights were elevated at 4, 24 and 72 hours after smoke inhalation. All elevations were statistically higher than normal. (Bottom) Lung per cent water was elevated at 4, 24 and 72 hours after smoke inhalation; however, gross pulmonary edema was unusual. *indicates statistically significant difference from control value ($P<0.05$)

and per cent of water were stable by 4 hours. The changes were minimal and do not represent frank pulmonary edema. Only 4 dogs of the entire group of 39 dogs used in the experiment had frothing pulmonary edema or lung weights more than 1½ times normal (18 gm/kg). Profound respiratory insufficiency was not present until at least 48 hours, and pulmonary edema was unusual.

Pulmonary dysfunction is reflected as a progressive increase in alveolar-arterial Po_2 gradient and a decrease in compliance (Fig. 2). Maximal ΔA-a Po_2 occurred at 24 hours. The ΔA-a Po_2 was significantly higher at 24 hours than at 2 hours ($P<0.05$). Compliance also deteriorated with time and was lowest at 72 hours. The injury progressively worsened over the first 24 hours.

Similarly, arterial Po_2 fell progressively from injury until 24 hours; Pco_2 was abnormally high only at 30 minutes after inhalation of smoke. That the increased Pco_2 was not attributable to hypoventilation at this time is shown by the increased respiratory rate and minute volume (Fig. 4). The animals continued to hyperventilate (increased minute volume) for at least 24 hours. The increased minute volume was primarily the result of increased tidal volume as rate tended to return to normal levels. Alterations in minute volume were not related to arterial Po_2 Pco_2 or pH (Fig. 5).

The ratio of dead space to tidal volume (Vd/Vt) was abnormal only at 30 minutes, returning rapidly to control values (Fig. 5).

Cardiac output was decreased for the first 24 hours (Fig. 6). At 30 minutes the cardiac output was profoundly lowered, being less than one third of control. The lowered cardiac output was accompanied by slight but unsustained hypotension. Both systemic and pulmonary vascular resistance (Figs. 6 and 7) were substantially elevated for prolonged periods. Whereas MAP fell slight-

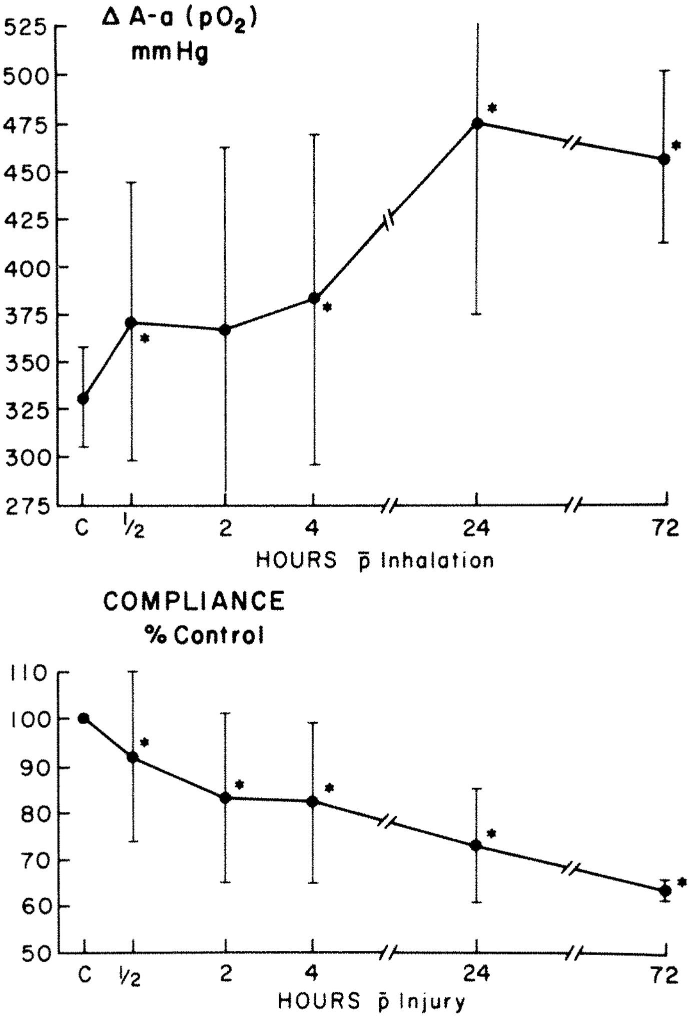

FIG. 2. (Top) Alveolar-arterial Po_2 differences rose consistently until 24 hours after smoke inhalation, then stabilized at that level. (Center) Compliance consistently decreased after injury, reaching its lowest level at 72 hours. *indicates statistically significant difference from control value ($P<0.05$).

ly, PAP was elevated during the first 4 hours. Atrial (PWP) pressures did not change significantly. Smoke inhalation produced a progressively worsening pulmonary condition and an early but abating cardiovascular dysfunction.

Histologic examination showed minimal lung damage. There was spotty but sparse alveolar edema, little if any destruction of lung architecture and minimal smoke particles in the alveoli. Figure 8 depicts one of the more severely affected areas from a lung taken 24 hours after injury. Some edema, some alveolar destruction and considerable congestion with blood and inflammatory cells are present.

Because most patients with burns receive substantial loads of crystalloids, the effect of a crystalloid load on smoke inhalation injury was examined. The results are tabulated in Table 3. There was essentially no difference between those dogs receiving Ringer's lactate and those which did not at 4 hours. The animals received a positive load (volume infused − urine output) of 1087 ± 290 ml depending upon weight. This is a load of about 54 ml/kg or the equivalent of nearly 4 liters to a 70 kg man at a rate of 1 liter per hour. There was a slight increase in lung weight and per cent water, but pulmonary edema was clearly absent both grossly and histologically. Cardiac output failed to respond to this fluid load, and vascular resistance remained elevated.

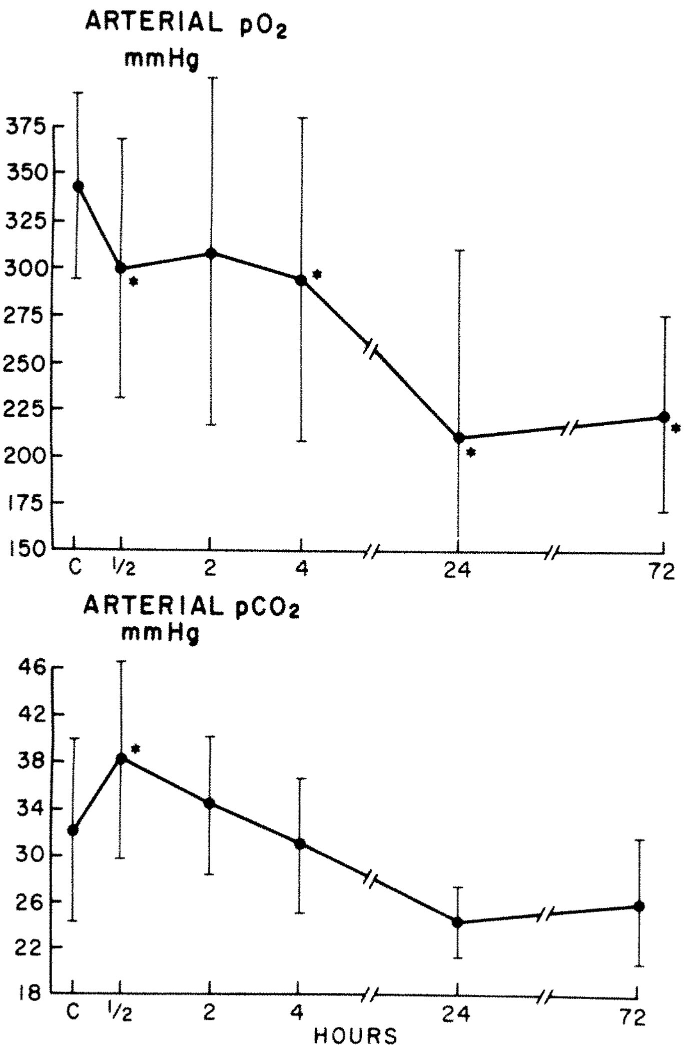

FIG. 3. (Top) Progressive decline of the arterial P_{O_2} occurred until 24 hours after smoke inhalation. (Bottom) Serial arterial P_{CO_2} measurements showing initial rise immediately after smoke inhalation, with subsequent return to normal values by 4 hours. *indicates statistically significant difference from control value ($P<0.05$).

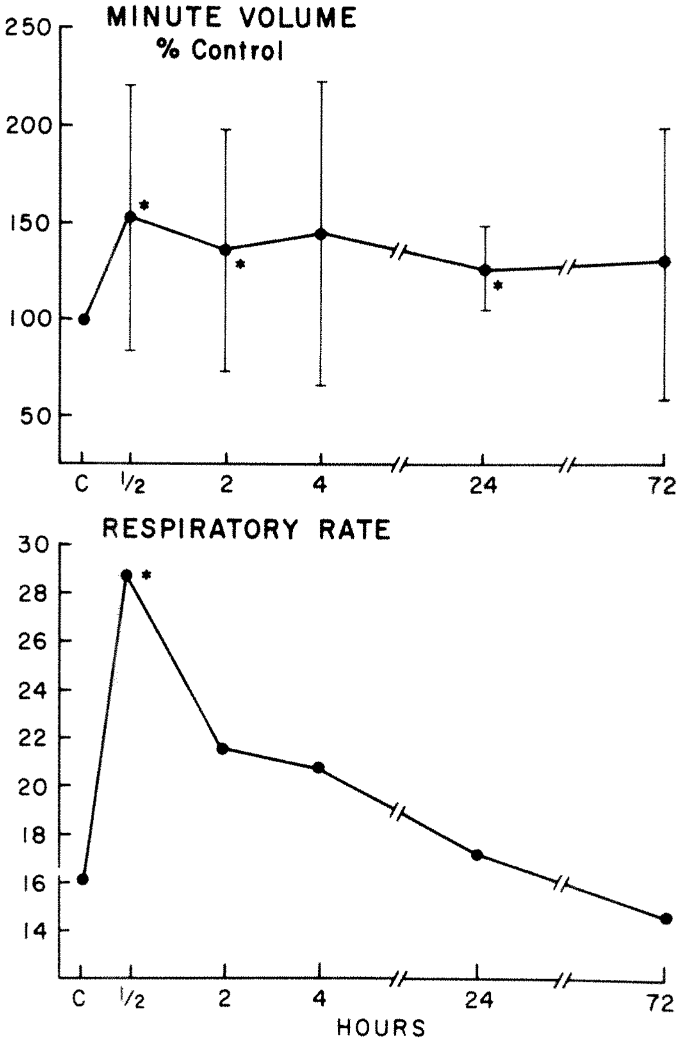

FIG 4. (Top) Serial minute volume measurements showed initial and persistent elevation after inhalation of smoke. (Bottom) Respiratory rate measured over 72 hours showed initial increase with gradual return to control level. *indicates statistically significant difference from control value ($P<0.05$).

Figure 9 shows that arterial P_{O_2} is responsive to volume ventilation. (In several dogs arterial P_{O_2} was measured while the animals were ventilated with the Harvard respirator.) The P_{O_2} is significantly lowered during the first 2 hours both with spontaneous and assisted ventilation. At 24 hours, the P_{O_2} became responsive to ventilation even though it was depressed with spontaneous re-

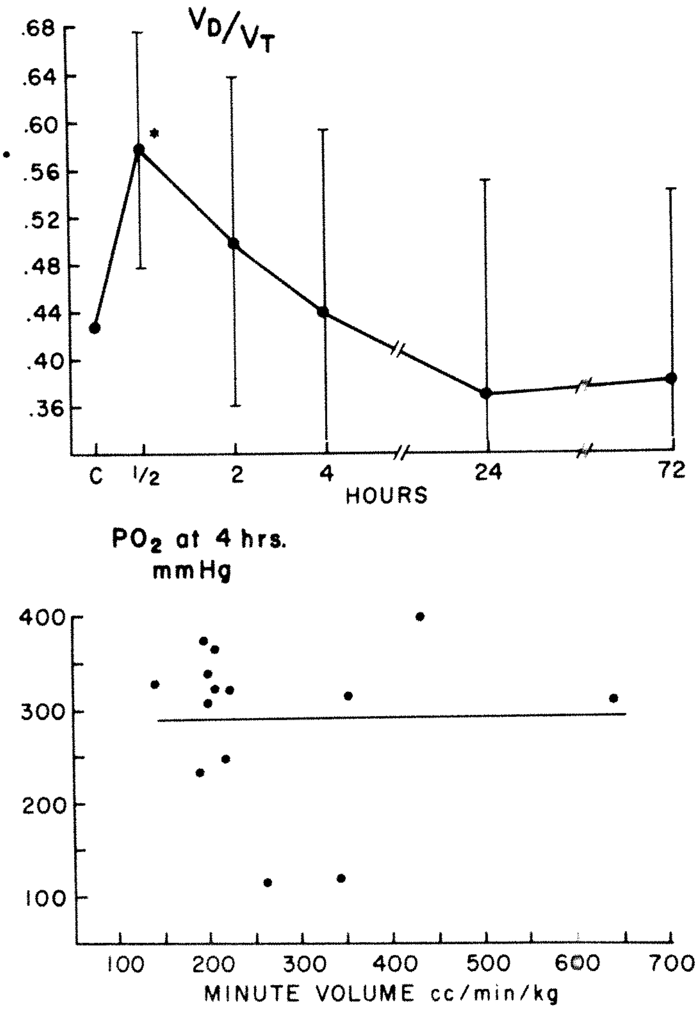

FIG. 5. (Top) Serial measurement of physiologic dead space showed an initial increase after injury with subsequent return to control levels. (Bottom) Relationship of arterial P_{O_2} to minute volume at 4 hours. There is no correlation of P_{O_2} to minute volume. *indicates statistically significant difference from control value ($P<0.05$).

spiration. Apparently, despite increased minute volume, the dog cannot overcome the primary pulmonary deficit produced by smoke inhalation. Figure 5 shows no relationship between increased minute volume and arterial P_{O_2} at 4 hours. This implies that the dogs hyperventilate despite satisfactory P_{O_2}. As these animals were not truly hypoxic (breathing 100% oxygen) the failure to decrease minute volume with elevated P_{O_2} suggests abnormal neural mechanisms. As P_{CO_2} and pH were normal at this time, the mechanisms remain somewhat obscure.

The effects of bacteria upon the smoke-injured lung form a separate study.[4] Suffice it to say, that when bacteria are placed intratracheally, not only did profound respiratory dysfunction occur, but mortality was increased.

In addition to the lack of pulmonary edema, gross examination of the respiratory organs disclosed that upper airway obstruction was absent. Laryngeal edema was not present, as also evidenced by the prolonged survival of the animals to at least 72 hours. The trachea and bronchi did show evidence of increased mucoid secretions, and soot was recovered from major bronchi.

Discussion

Sequentially, the injury can be divided into four stages (Table 4) with alterations in respiratory, cardiovascular and neural function occurring in each phase.

Stage I is the period in the smoke chamber. The animals spontaneously inhaled smoke without evidence of glottic closure. An immediate hyperventilation occurred with increase in rate. At 5 minutes, the P_{O_2} was severely depressed, P_{CO_2} was quite high and acidosis was present. Some bronchospasm existed. Apnea tended to occur. It

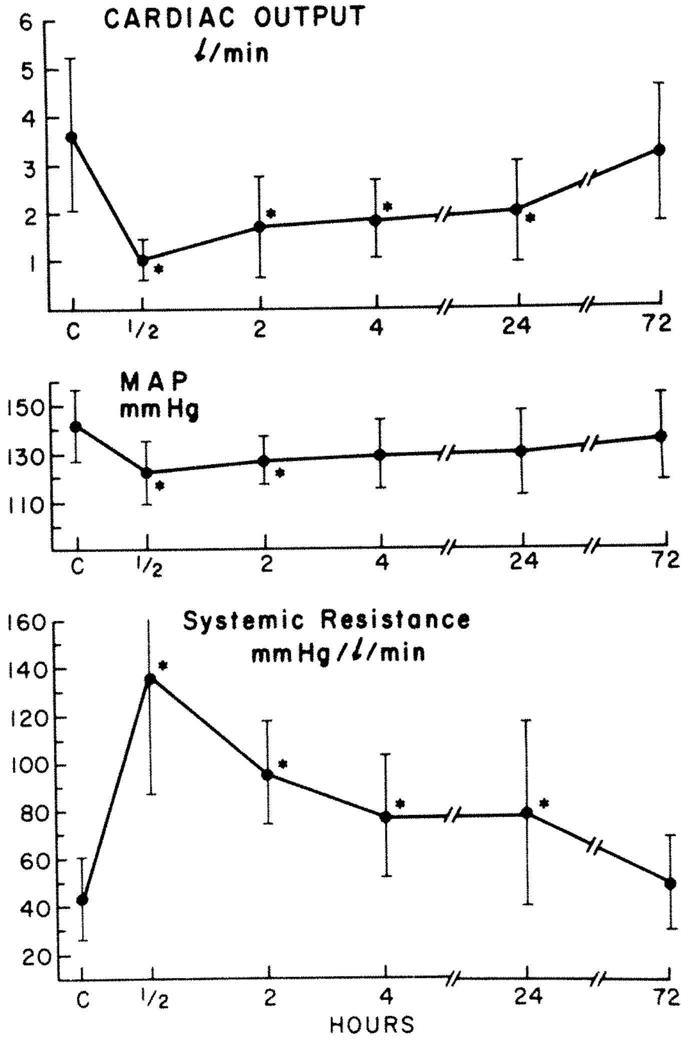

FIG. 6. (Top) Serial cardiac output measurements showing initial and sustained decrease with return to control values in surviving dogs at 72 hours. (Center) Mean arterial blood pressure showed initial, but transient, drop with return to control levels by 4 hours. (Bottom) Systemic resistance was elevated over the first 24 hours after inhalation of smoke but returned to control level by 72 hours. *indicates statistically significant difference from control value ($P<0.05$).

is likely that the cardiac output is depressed, probably because of inhalation of toxic products such as carbon monoxide. Probably, the elevated P_{CO_2} is as much attributable to inhaled CO_2 as to effective hypoventilation. If respiration is not assisted, the animal dies. The anesthetized animals breathed smoke freely, a response which is abnormal as glottic closure tends to occur with inhalation of noxious products in awake animals and man. Once the animal is "overcome," i.e., unconscious, it will inhale smoke for at least several minutes. Extension of this observation to man implies that near-unconsciousness must occur before significant smoke inhalation.

Stage II is the immediate period up to 30 minutes. At 30 minutes, injury was apparent from severely depressed cardiac output, profoundly increased vascular resistance, hypercapnia, and increased physiologic dead space. Slightly lowered arterial P_{O_2} arterial blood pressure and minimally decreased compliance were present. Hyperventilation, primarily achieved by increased rate, was profound. This series of events occurred most likely because the increased pulmonary vascular resistance caused blood to flow only through a small portion of the lung, which was ventilated. Such a situation results in increased physiologic dead space (Vd/Vt) and increased P_{CO_2} despite hyperventilation. What little blood does pass through the lung, however, is oxygenated. Bronchospasm is apparently minimal as evidenced by increased Vd/Vt but a slight decline in compliance. Pulmonary arterial pressure is elevated as a result of increased vascular resistance.

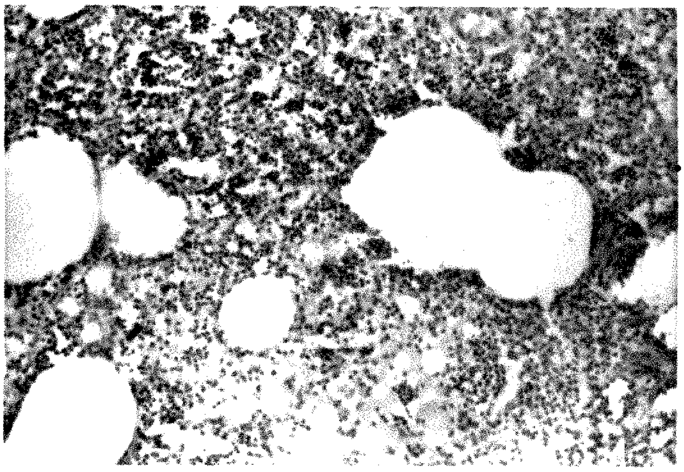

FIG. 8. Histologic section of the lung of a dog subjected to smoke inhalation taken 24 hours after injury. Alveolar destruction, congestion, and inflammatory cells can be seen. This is a localized section, the majority of the lung tissue was normal.

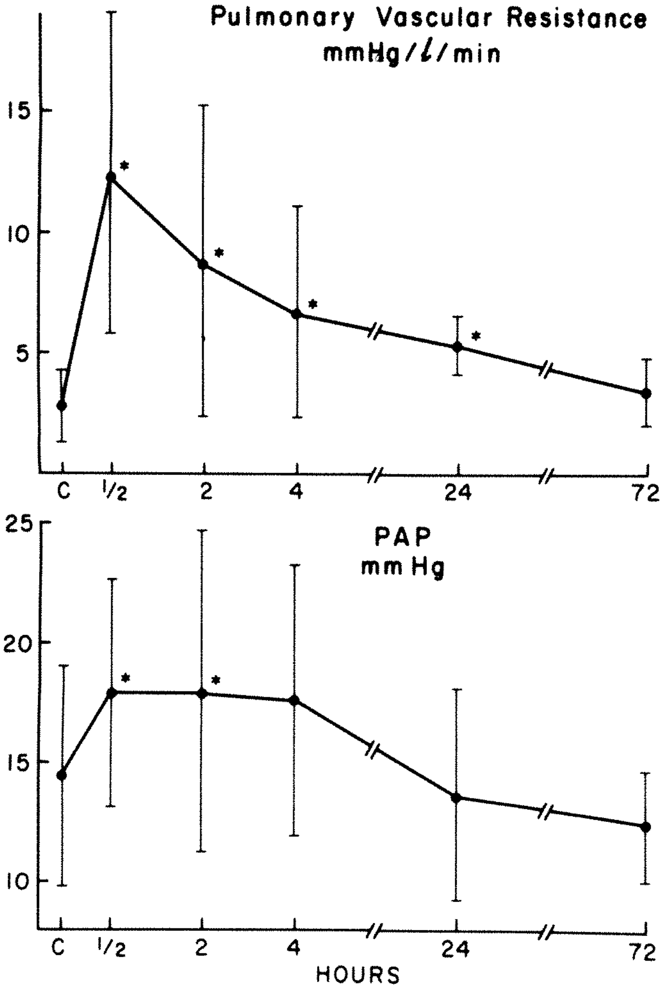

FIG. 7. (Top) Prolonged elevation of the pulmonary vascular resistance occurred with return to control levels at 72 hours after injury. (Bottom) Pulmonary artery pressure was increased only transiently with control levels reached 24 hours after inhalation of smoke. *indicates statistically significant difference from control value ($P<0.05$).

Decreased cardiac output probably results from inhaled toxins such as carbon monoxide, but could be caused by increasingly severe acute pulmonary vascular resistance (PVR). Several possible mechanisms are suggested for the development of this increased PVR. Moss and co-workers[9] showed elevation of PVR attributable to cerebral hypoxia. Certainly, during inhalation this condition exists. Secondly, a profound increase in circulating epinephrine, occurring in response to stress, could lead to elevation of TPR and PVR[2] and might explain the lack of bronchospasm at this stage.

Clinically, the early stage would be suggested by elevated respiratory rate, *increased* P_{CO_2}, mild-to-moderate hypoxia, signs of low cardiac output with peripheral constriction and signs of smoke inhalation such as tracheal soot and singed nasal hair. The chest x-ray examination is probably normal.[8]

As carbon monoxide is expelled and the cardiovascular system returns toward normal resistance, Stage III develops. As blood flow increases through the lung, alveoli become ventilated and perfused, resulting in exhalation of CO_2 and lowering of the Vd/Vt. However, the blood

TABLE 3. *Comparison of Dogs Receiving Fluid Load With Those Not Receiving Fluid After Smoke Inhalation*

Variable	Normal	Smoke Only 4 hrs	P vs. Normal	Smoke + Ringer's Lactate 4 hrs	P vs. Normal	P vs. Smoke Only
Δ (A-a) P_{O_2}	332 ± 47*	384 ± 86	.05	383 ± 90	.05	NS
Arterial P_{O_2}	343 ± 48	294 ± 86	.05	286 ± 91	.05	NS
Arterial P_{CO_2}	32.3 ± 7.9	31.0 ± 5.4	NS	35.3 ± 8.6	NS	NS
Respiratory Rate	16.1 ± 7.0	20.8 ± 15.5	NS	20.8 ± 9.7	NS	NS
Minute Volume (%)	100	144 ± 78	NS	120 ± 33	NS	.05
Compliance (%)	100	82.2 ± 17.2	.05	76.3 ± 22.4	.05	NS
Vd/Vt	0.43 ± .12	0.44 ± .15	NS	0.44 ± .12	NS	NS
Lung Weight (gm/kg)[5]	12.4 ± 1.3	14.8 ± 1.8	.05	16.3 ± 1.6	.05	.05
Lung H_2O (%)[5]	79.0 ± 1.3	81.5 ± 1.8	.05	83.6 ± 1.8	.05	.05
Cardiac Output (l/min)	3.62 ± 1.61	1.88 ± .79	.05	1.72 ± .61	.05	NS
MAP	142 ± 15	128.2 ± 14	.05	130.7 ± 14.3	.05	NS
TPR	44.9 ± 17.3	77.1 ± 25.7	.05	79.2 ± 17.7	.05	NS
PAP	14.4 ± 4.6	17.5 ± 5.6	.05	13.3 ± 3.0	NS	NS
PVR	2.8 ± 1.5	6.6 ± 4.5	.05	5.2 ± 2.9	.05	NS
Fluid load	———	0	———	1087 ± 290 Δ	———	———
4-hr urine output	———	———	———	209 ± 88 Δ	———	———

*Numbers following ambiguous signs are standard deviations of the mean.

flow is exposed to injured alveoli. Like any tissue, this injured lung will respond by local edema formation. The water in such edema is derived from plasma water. Over a period of hours, the edema, probably interstitial in nature, produces alveolar closure with continued capillary perfusion. The lung also reacts to injury by congestion and inflammation (Fig. 8). Compliance begins to decrease, probably because of three factors: 1) interstitial edema 2) decreased surfactant (vide infra) and 3) some degree of atelectasis and/or bronchospasm. Decreased compliance and increased vascular resistance lead to altered ventilation perfusion ratios and continued increase in ΔA-a P_{O_2}. That a primary source of hypoxia is attributable to mechanical factors and not diffusion problems is reflected by the return toward normal arterial P_{O_2} with mechanical ventilation. The sporadic nature of the injury in the lung is evident by several observations: 1) profound hypoxemia was unusual; 2) histologic examination showed only spotty damage; and 3) recent work by Moylan et al.[8] with ^{133}xenon scanning showing a spotty distribution of scanning defects in smoke-injured man. It is probably the spotty nature of the injury which has caused so much confusion concerning this injury. The lung has a large functional reserve and can overcome such scattered minor injury when looked at grossly, as done in this experiment, or by clinical chest roentgenogram.[8]

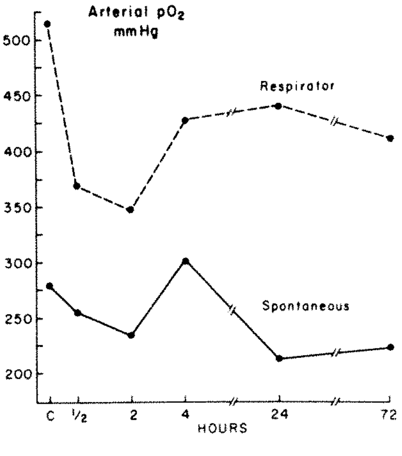

FIG. 9. Comparison of changes in arterial P_{O_2} in dogs on ventilator and dogs breathing spontaneously. Mechanical ventilation easily reversed the hypoxemia after 2 hours.

Clinically, Stage III is evident by increasing hypoxemia, normal P_{CO_2}, hyperventilation, some evidence of lowered cardiac output and "stiffening" of the lung. Uncomplicated smoke inhalation is apt to be easily treatable in the first 24-48 hours by volume ventilation.

Apparently, Stage III is unaffected by massive fluid infusion consisting of crystalloid, although some increase in lung water did occur. The increase in lung water is probably a distributional phenomenon. Interstitial edema from crystalloid infusions is, however, exaggerated by lung injury.[6] Again, frothing pulmonary edema was not seen, and pulmonary function not altered. Clinically, if heart failure occurs or if fluid loads exceed the level used in this experiment, more profound pulmonary edema may complicate smoke inhalation.[12]

Stage IV occurs between 24 and 72 hours. Because the lung is injured, it becomes more susceptible to bacterial infection.[4] Severe pulmonary insufficiency is easily produced in the smoke-injured dogs if sub-lethal doses of Pseudomonas are injected intratracheally. In these animals, the full picture of pulmonary edema, destruction of lung tissue, profound hypoxemia and respiratory death, frequently associated with smoke inhalation, was produced. In the present study the animals that died spontaneously showed evidence of bacterial pneumonia (Fig. 10), and Pseudomonas, Streptococci, Staphylococci and

E. coli were cultured from the lung. Stage IV, bacterial pneumonia superimposed upon smoke injury, is probably the stage viewed clinically as respiratory failure. The rapidity of development of bacterial pneumonia in burned patients is probably attributable to the lung injury to reduced bacterial clearance of the lung resulting from the burn.[15]

Examination of the standard deviations derived in the present experiment discloses a wide range of values of most variables. There are two reasons. First of all, in the absence of an endotracheal tube, the amount of inhaled smoke reaching the lung was not consistent. Dogs with elongated nasal passages, with epiglottic closure or early bronchospasm may have protected the lung from substantial inhalation of smoke. Secondly, physiologic data of the type obtained exaggerate the functional capability of the lung. It is obvious that the extubated animal more closely resembles the clinical situation than inhalation through a tube or tracheostomy. By inference from the literature to date, predictability of lung injury from any set of variables is lacking.[1,8,16] Until a study of the distribution of smoke in the lung is accomplished, this problem will not be solved.

Moritz et al.[10] discussed the distribution of injury from heat, flame and steam inhalation in intubated dogs. In contrast to the present study, tracheal edema probably related to heat was found. These investigators described injuries primarily involving the central alveoli and small bronchi. Lung damage was not dependent on the inhaled heat, but was related to infection after 48 hours.

Stone and others[17] showed that experimental mortality from inhalation of heat depended upon the oxygen content and humidity of the inspired air. Antibiotics failed to modify a high mortality rate. Unlike the present study, the whole animal was exposed to heat. It is not possible from their work to separate the effects of total body heat exposure from respiratory burn.

TABLE 4. *Stages of Inhalation Injury*

Stage I: During Smoke Inhalation
  Hypoxemia, hypercapnia, acidosis
  Low cardiac output
  Hyperpnea decreasing to apnea
  ? Bronchospasm
  Carbon monoxide poisoning
  Unconsciousness
Stage II: Immediate Period
  Hypercapnia, mild hypoxemia
  Severely depressed cardiac output
  Severe vascular constriction
  Increased Vd/VT
  Hyperventilation
  Carbon monoxidemia
Stage III: Progression of Injury (2-24 hr)
  Increasing hypoxemia
  Decreasing compliance
  Vd/Vt normal
  Cardiovascular status tends to normal
  Edema formation in lung
  Hyperventilation
  Lung failure absent
Stage IV: Pulmonary Failure or Recovery
  Bacterial pneumonia → Lung failure
  No bacterial pneumonia → Recovery

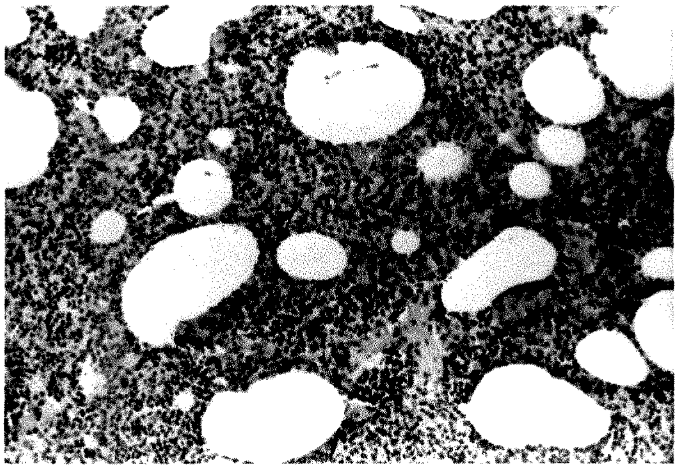

FIG. 10. Lung section taken from a dog that died between 48 hours and 72 hours after smoke inhalation with gross and bacteriologic evidence of pneumonia. Marked alveolar destruction, severe congestion and edema are present.

More recently, Zikria and co-workers[18] demonstrated in the laboratory that inhalation of noxious substances, particularly aldehydes, are probably of more importance than smoke or heat inhalation. As opposed to our findings, inhalation of wood smoke produced profound pulmonary edema. The only difference between the experiments was the use of endotracheal tubes during inhalation of Zikria's group. This implies that the severity of injury is dose-related.

Clinically, it is difficult to separate the respiratory effects of hypovolemic shock[5] and the burn wound[14] from inhalation injury. Robinson et al.[14] have correlated decreased arterial P_{O_2} vital capacity and FEV_1 with burn area in man. These gas and ventilation changes are similar to those produced experimentally. Garzon and associates[7] showed decreased compliance and increased work of breathing in early inhalation injury. Their patients were also burned. Phillips and others[11] documented pulmonary edema, atelectasis and spotty distribution of inhalation injury in man. These authors discussed the importance of the altered ventilation perfusion ratios resulting from the injury. They also noted that clinical evidence of airway infection was present by 48 hours in their patients.

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Letters to the Editor

February 24, 1975

Dear Editor:

The paper by Hines et al., describing a new technique of double pyloroplasty as an adjunct to vagotomy in the surgical treatment of peptic ulcer disease (Annals of Surgery, 181:1:40, 1975) must be examined critically in the light of recent convincing evidence that bile, refluxing into the stomach, may not be as innocuous or beneficial as once believed.[4]

The authors feel that "most failures (following vagotomy and pyloroplasty for peptic ulcer) are due to poorly emptying pyloroplasty," but they present no evidence to support their contention. It is true that an inadequate pyloroplasty plus truncal vagotomy may produce difficulty in gastric emptying, cause stasis and recurrent ulceration. However, critical reviews of most series of vagotomy and pyloroplasty suggest incomplete vagotomy, rather than incomplete emptying caused by a poorly fashioned pyloroplasty, as the major cause for recurrence.[2,6] Both theories may, in fact, be incorrect.

It has been pointed out that any operative procedure which destroys, shunts, excises or by-passes the pyloric sphincter,[3] and permits bile to bathe the gastric antrum, damages the integrity of the mucosal barrier and permits back diffusion of H^+.[1] This sets the stage for the development of reflux bile gastritis or gastric ulceration.[4] It is now being more widely accepted that reflux bile gastritis may actually be the cause of many of our, so called, post gastrectomy and post pyloroplasty syndromes.[5]

If this is even remotely possible, then the procedure of double pyloroplasty, which renders the pyloric sphincter even more incompetent than the more classic Weinberg modification of the Heinecke-Mikulicz technique may, in the long run, expose the patient to an increased risk of developing gastric ulceration or a bile reflux gastritis syndrome and its sequelae.

The pyloric sphincter is nice to have–it prevents dumping and bile reflux. Physiologically it serves a useful purpose and it may well be, to paraphrase an old saying, that "half a sphincter is better than none".

The final chapter is yet to be written in the surgery of peptic ulcer disease.

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March 12, 1975

Dear Editor:

Thank you for the opportunity to read and reply to Doctor Murry Fischer's letter. We share Doctor Fischer's concern about reflux "alkaline" gastritis causing epigastric pain, bilious vomiting, the dumping syndrome, and even recurrent peptic ulceration. However, most of the patients with this syndrome have had Billroth II hemigastrectomy or gastroenterostomy, usually without vagectomy. The time lapse in most series is about 5 years from the operation to onset of symptoms. Any patient who has had an operation that either alters pyloric function or bypasses the pylorus is theoretically subject to this syndrome, and this, of course, includes 95% of all patients who have had peptic ulcer surgery.

Contrary to Doctor Fischer's statement, there is a great deal of evidence that poor gastric emptying or outlet obstruction contributes to recurrent peptic ulcer.[1-4] The whole idea of the Weinberg closure is to reduce gastric stasis and the effectiveness of this procedure is well established.

We have operated upon 96 patients using truncal vagotomy and double pyloroplasty and have followed these patients from one month to 5 years with an average followup of three years. At the time of this writing we have had one patient with probable recurrence of ulcers, 5 patients with minimal dumping syndrome and 4 patients with loose stools. Epigastric pain, bilious vomiting and anemia have not been encountered. Fortunately, our concern about reflux gastritis has not materialized but we will continue to watch for it. We are pleasantly surprised at our low recurrence rate and the minimal untoward postoperative sequelae that has been encountered.

James R. Hines, M.D.
Professor of Surgery
Northwestern University Medical School
Chief of Surgery, Wesley Pavilion
Northwestern Memorial Hospital
Chicago, Illinois 60611

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June 30, 1975

Dear Editor:

In the issue of Annals of Surgery, May 1975, Volume 181, No. 5, Page 784, Woodward cites poor results following dilatation of the esophageal strictures encompassing an experience of 39 patients operated upon between 1953 and 1963. In this series he cites a high recurrence rate of both hiatal hernia and stricture, half the patients requiring prolonged bougienage or further surgical procedures.

During this period of time, it is apparent that Dr. Woodward was using the treatment of hiatal hernia, herniaplasty and advocating pyloroplasty rather than an anti-reflux procedure.[1] Hence his results are not comparable to those achieved by Harrington et al. now described in the same issue of Annals of Surgery.[2] His advocacy of the Thal-Nissen patch graft should be considered in this light. Incidentally, pyloroplasty as used by Woodward then could increase the problem further with alkaline reflux following destruction of the "Keeper of the Gate" (Greek-pyloros).

Lawrence Braslow, M.D.
Arlington Medical Center
Riverside, California 92503

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July 8, 1975

Dear Editor:

Dr. David Tice has called to our attention an error in the text and in Table 2 of our paper published in the May 1975 issue of the Annals of Surgery. We reported a patency rate of 20% (5 of 25) in 25 femoral popliteal bypasses using preserved saphenous vein homografts. This conclusion was based on a misinterpretation of the text and of Table 3 in his paper (Surgery 72: 260, 1972). The correct figure was a patency rate of 52% (13 of 25) of grafts followed for one year and 84% (7 of 8) followed for longer than one year.

Jere W. Lord, M.D.
New York, New York

Book Reviews

Handbook of Pediatric Surgical Emergencies. Diller B. Groff, 176 pages, Flushing, Medical Examination Publishing Co., 1975, $10.00.

THIS READABLE MANUAL provides a convenient reference for medical personnel not experienced in the management of the more common pediatric surgical emergencies. Although there are brief prefaces on incidence and etiology, discussion is wisely limited to the basics of saving life rather than attempting to teach the reader pediatric surgery. In the first of four sections, the discussion of abdominal emergencies such as intestinal obstruction and omphalocele is generally accurate and helpful, although thoroughness and sometimes accuracy are occasionally sacrificed to brevity, most noticeably in the passages on volvulus and rectal bleeding. Some of the black and white photographic illustrations lack contrast and add little to the text.

The second section on newborn respiratory emergencies is well organized, concise, and well illustrated. The description of air-block syndrome is particularly good.

In the third section on childhood emergencies, Groff includes a sensitive approach to the examination of the child with appendicitis, a well illustrated discussion of barium enema reduction of intussusception, a practical guide to management of incarcerated hernia, a good discussion of burns, and a first-rate description of the battered child syndrome. Discussion of trauma and of G.I. bleeding is limited and somewhat sketchy.

The last and best section contains a wealth of practical detail on basic techniques including fluid and electrolyte management, umbilical vessel catheterization, endotracheal intubation and mechanical ventilatory support among many others, and makes excellent use of simple tables, line drawings and photographs.

This handbook of life-saving procedures for the pediatric surgical patient with emphasis on the newborn should be a welcome addition to the emergency reference library of community hospitals.

ANTHONY SHAW, M.D.

The Systemic Manifestations of Inflammatory Bowel Disease. W. M. Lukash and R. B. Johnson, Editors, 356 pages, Springfield, Charles C Thomas, $15.00.

DRS. LUKASH AND JOHNSON have successfully carried out the difficult task of collating a series of talks into a very readable book on the timely topic of inflammatory bowel disease. The title of the book is actually misleading, since the various authors have considered the much broader topic of etiology, clinical manifestations, signs and treatment of the disease. While systemic manifestations are emphasized throughout the book as its major theme, they in no way dominate or are detrimental to the text.

President Eisenhower's struggles with regional enteritis is a dramatic way to introduce the subject. Curiously enough, not much has been learned about the disease since the time of his illness over a decade ago. The authors are careful to document the extent of our knowledge in a factual, descriptive, and enjoyable fashion. The less common peripheral manifestations of the disease are especially well covered.

Discussion of the surgical management of toxic megacolon by an internist will be of special interest to the surgeon. The author presents data to support the notion that the initial management of such patients can be accomplished with supportive therapy and steroids. He further stresses that the high surgical mortality of this disease is a consequence of procrastination and therefore develops a set of guidelines for appropriate surgical intervention. Chapters on the surgical management of chronic ulcerative and granulomatous ileocolitis came at the end of the book, hopefully not as an afterthought. They are straight forward presentations of the current state of the art. Unfortunately, they do not incorporate any new material and are written primarily for students at the under graduate level.

All in all, the book is well written. For a multiauthored text, it flows in an orderly fashion and is quite complete in its coverage of this devastating disease. I would consider it a must for the surgeons bookcase.

FRANK G. MOODY, M.D.

Management of Surgical Complications. (3rd Edition). C. P. Artz and J. D. Hardy, 834 pages, Philadelphia, W. B. Saunders Co., 1975, $30.00.

THE EXPRESSED AIM of this third edition of a now familiar book is to provide the general surgeon with authoritative advice on the management of complications both in the operating room and during the postoperative period. Each of the 33 Chapters has been revised extensively to bring the subject matter up to date. Twenty new authors have been added; some to replace previous contributors and some to write new chapters on the complications of transplantation, and on postoperative neurosurgical problems. General surgeons may well miss, however, thorough handling of urological complications and problems following amputation and hand surgery found in earlier editions.

Illustrations throughout the book have been improved and are well chosen. The use of diagrams is particularly effective in the chapters on shock, cardiac surgery, transplantation, and anesthesia. The latter section is especially well done. The new chapter on transplantation complications is thorough with an excellent bibliography, but the discussion of neurosurgical complications is quite short, and might have been improved by illustrations and a more adequate bibliography. The chapter devoted to surgery of the esophagus and diaphragm, and the chapter on the lung are good. The former is followed by an extensive bibliography.

There is no part of the book devoted to trauma. With the increasing emphasis now being placed on the responsibility of the general surgeon in the care of accident cases, the inclusion of an overall discussion of this subject would have been helpful.

The book is well organized, easy to read, and should prove a valuable addition to any general surgeon's reference library.

WILLIAM S. MCCUNE, M.D.

Common Duct Stones. Frank Glenn, M.D., 135 pages, Springfield, Charles C Thomas, 1975, $11.50.

THE CONTENT of this monograph on common bile duct stones reflects the long interest and large experience of the author in the management of patients with this condition. Especially noteworthy is the discussion on the incidence of cholelithiasis and choledocolithiasis in the United States' population, and the historical aspects of common bile duct stones. Special emphasis is placed also on the contributions of radiologic diagnostic techniques in the clinical management of patients with choledocolithiasis. The major theme of the book, however, is a detailed discussion of the clinical manifestations and management of patients with common bile duct stones. There are, however, some major areas related to the overall subject of common bile duct stones which are, in this reviewer's opinion, inadequately covered. For example, there is only a brief reference to etiological factors involved in formation of biliary tract calculi. A review of the anatomy and physiology of the normal common bile duct and choledochal sphincter is not presented. The pathophysiology and bacteriology of cholangitis associated with stones in the common bile duct are only briefly discussed. Some of the important complications resulting from stones in the common bile duct are discussed in detail; others, however, are only briefly commented upon. For example, there is very little discussion of the effects of intermittent common bile duct obstruction and repeated attacks of cholangitis on liver function and alteration.

This somewhat abbreviated treatise on common bile duct stones is concise, practical, and presents much helpful clinical information related to the problem. This monograph, therefore, will be of most interest to practicing surgeons and gastroenterologists who are primarily concerned with patient management in this disease area.

WILLIAM H. SHINGLETON, M.D.

Fractures. (Vol. 1 and 2) Charles A. Rockwood, Jr. and David P. Green, 149 pages Philadelphia, J. B. Lippincott Company, 1975, $89.50.

The authors set out to provide a current fracture textbook that contains historical background, a complete list of references, a presentation of normal and pathological anatomy of joints and osseous structures, a discussion of alternate methods of fracture treatment with advantages and disadvantages of each, and finally, the personal preference of each contributor. In each of the 26 chapters these goals have been attained. The comprehensive list of references is particularly valuable for quick "literature consultation."

In this scholarly presentation, the 26 contributors have provided a consistent pattern in each chapter that is interesting and somewhat personal. Concepts have been presented by use of diagrams adjacent to the roentgenograms. Errors of treatment are emphasized as these are more important to the house officer than are the erudite discussions of primary open reduction. This may attract the surgeon.

All contributors have emphasized avoidable complications as well as a rational approach to acceptable initial or delayed treatment of a complex spine or extremity injury.

The illustrations throughout both volumes are superb in clarity and contrast. The Subject Index is complete and accurate and contains references to practically all pertinent articles in the world's literature as they relate to fractures and joint injuries.

Unfortunately, children's fractures and epiphyseal injuries are not included in these volumes. This is understandable but unfortunate. Pediatric fracture problems are different. The editors specified that these books cover adult fractures, but the reader must realize this and not seek information about epiphyseal injuries.

J. LEONARD GOLDNER, M.D.

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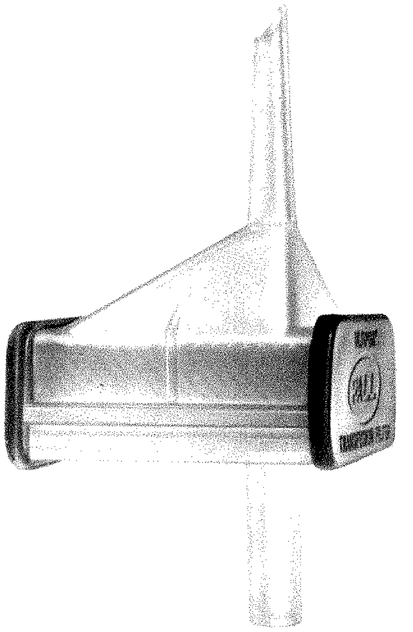

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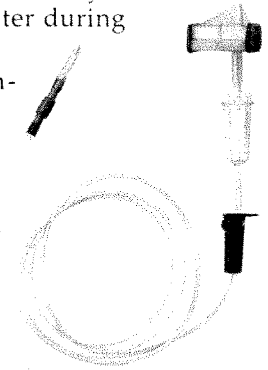

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**Archives of Surgery, 106:386-394, April, 1973.

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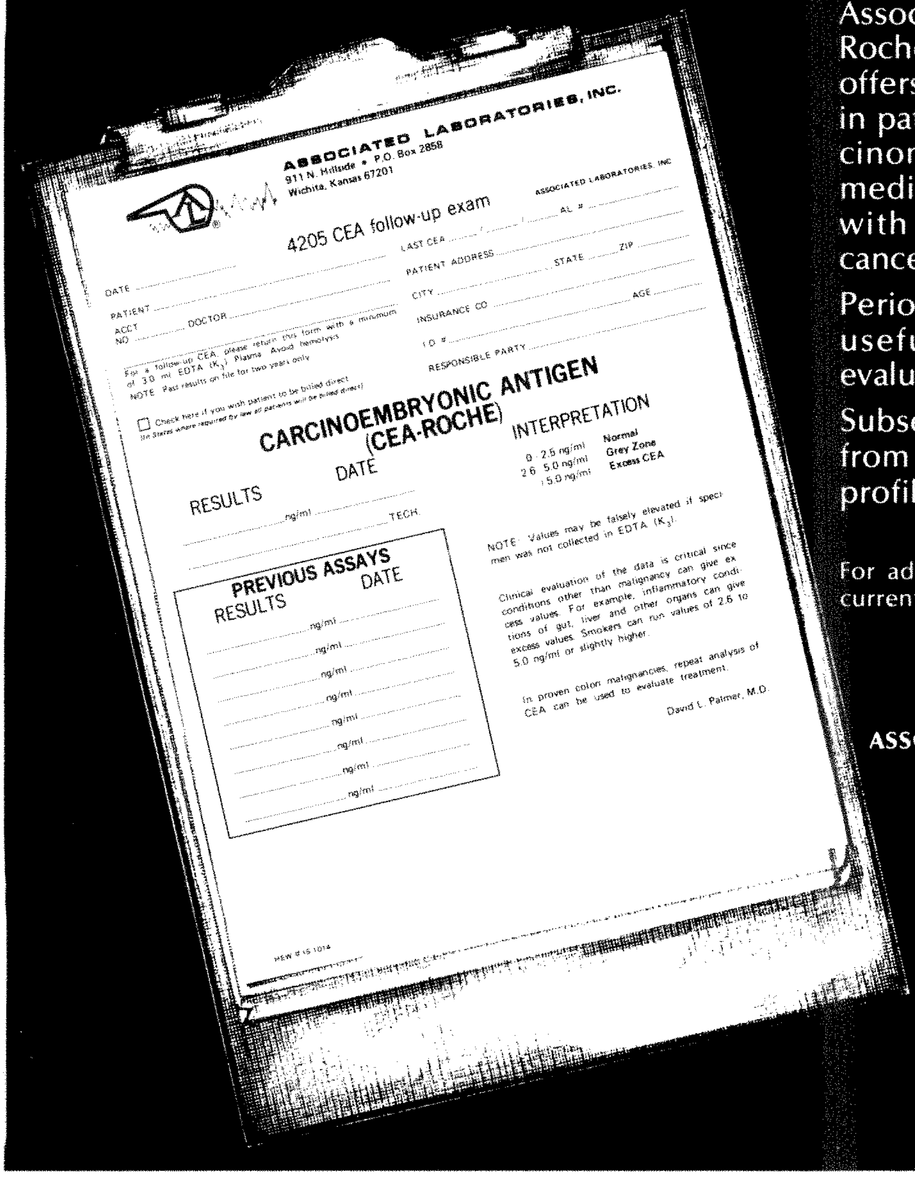

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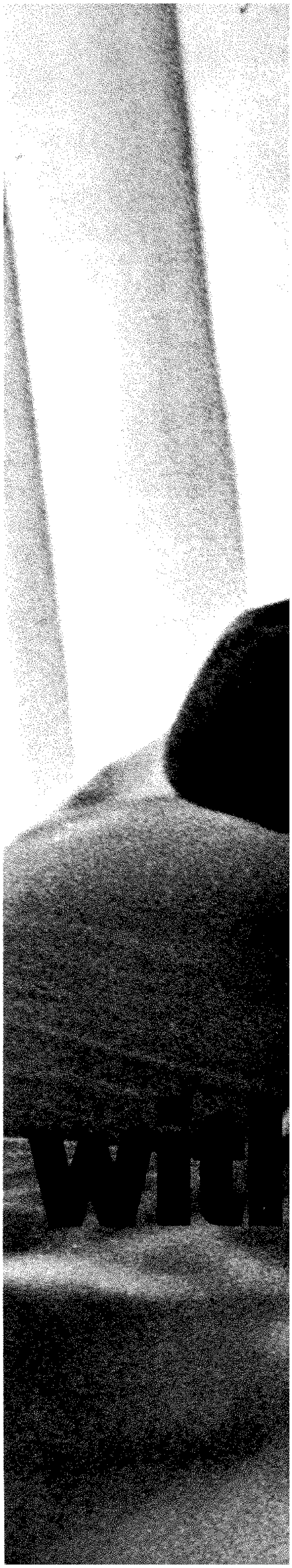

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PRECAUTIONS: During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

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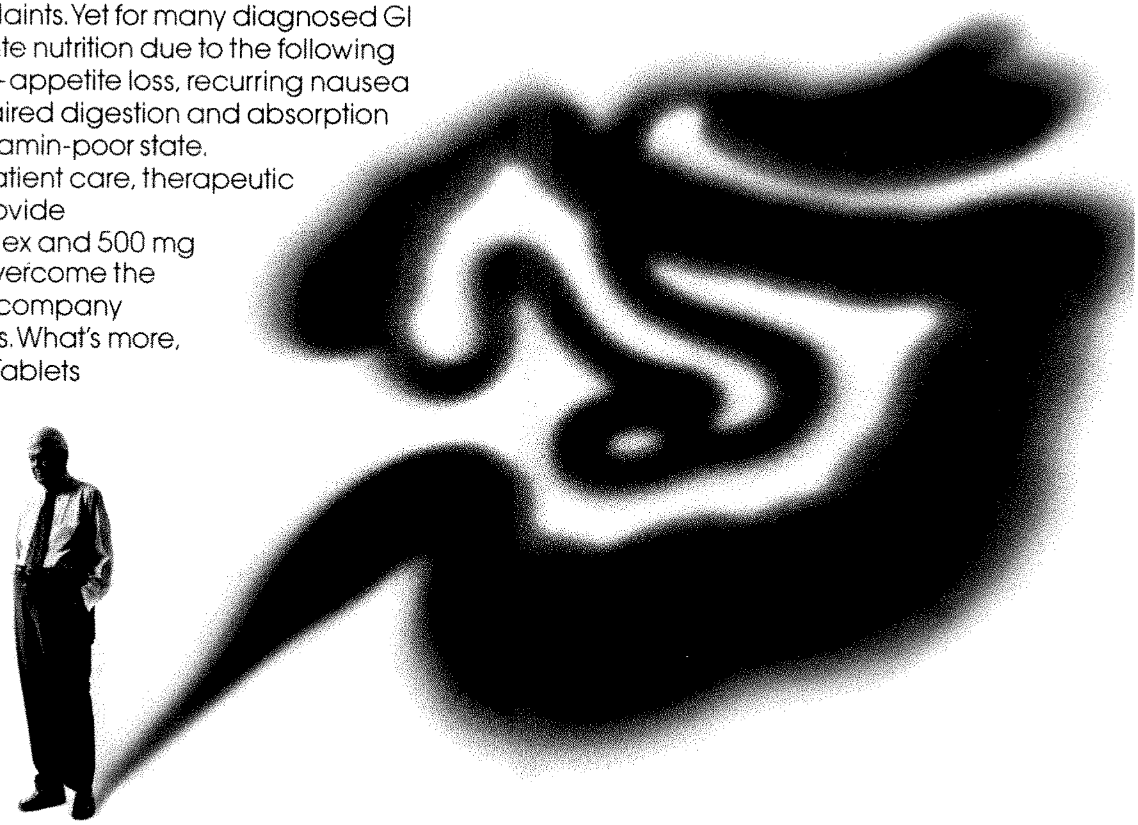

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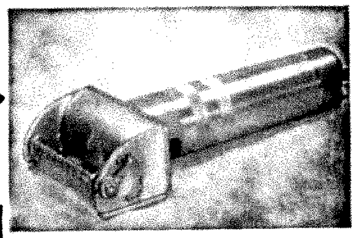

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INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS: *Drug Dependence:* Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Percodan, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, Percodan is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical oourse of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Serious overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of Percodan may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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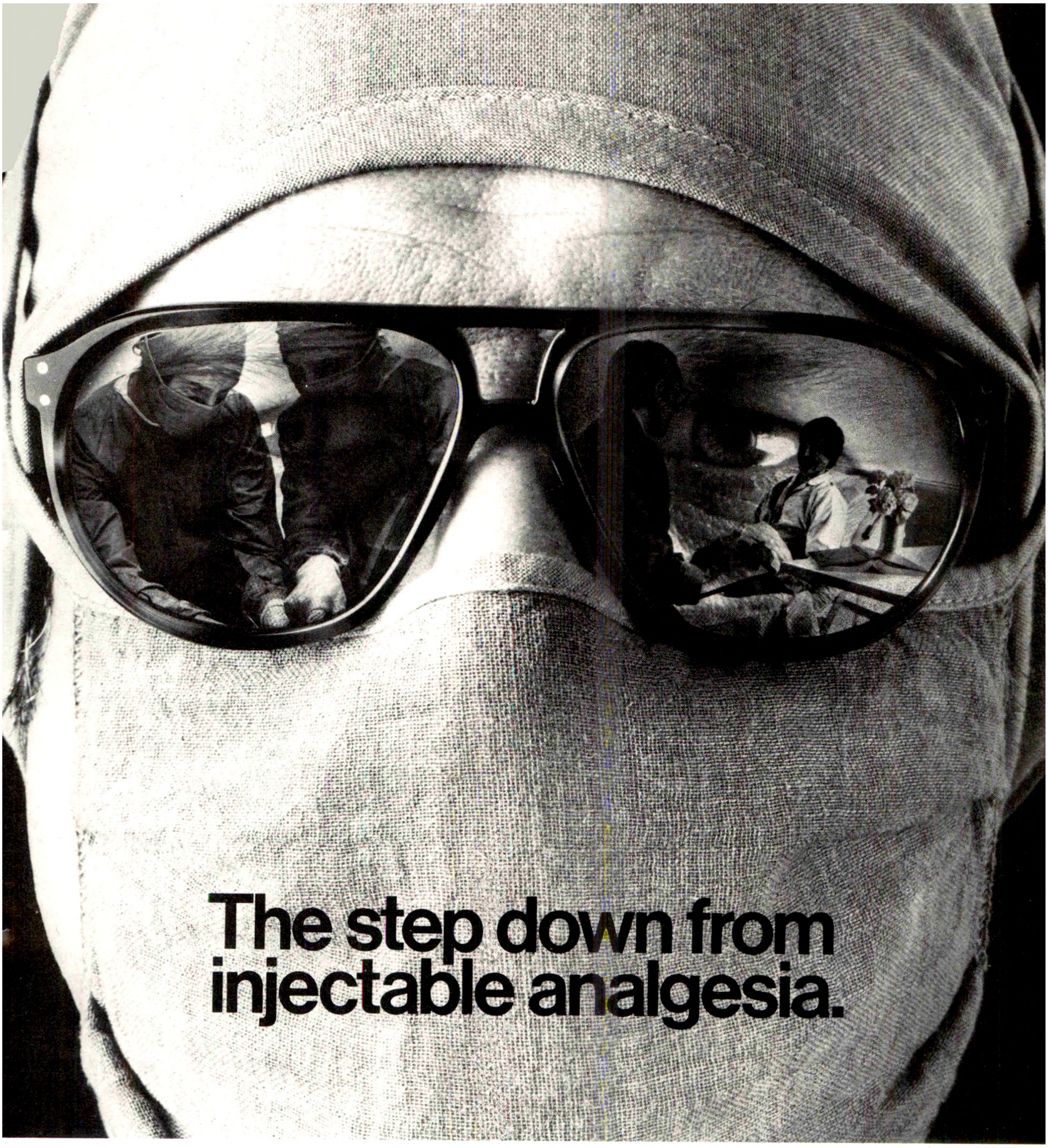
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*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

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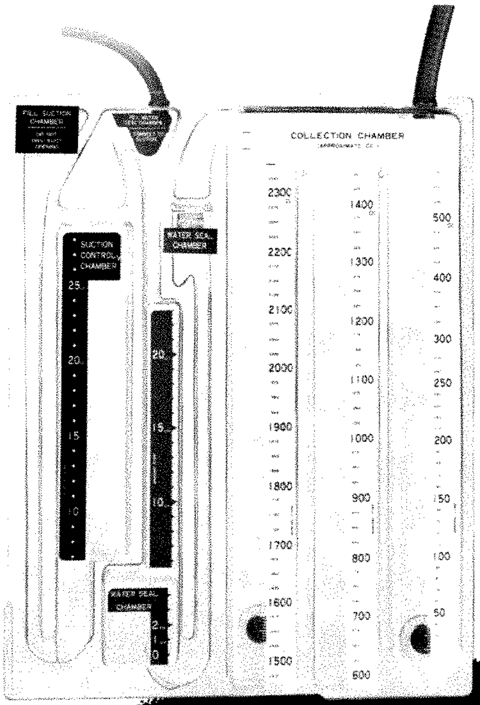

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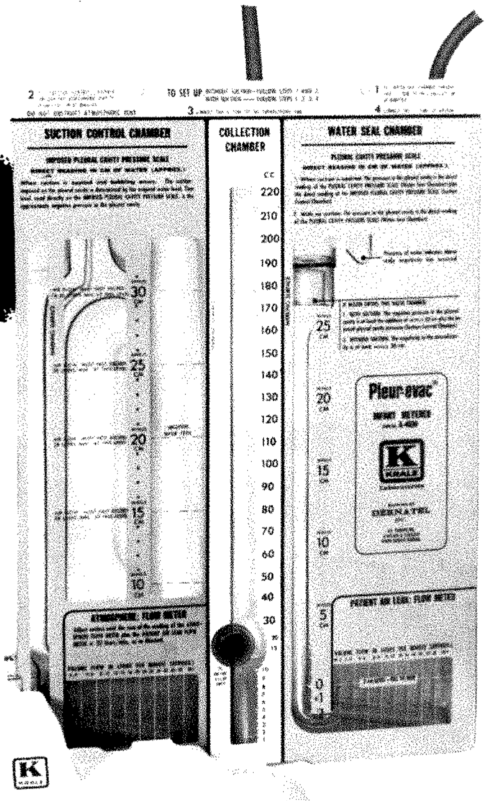

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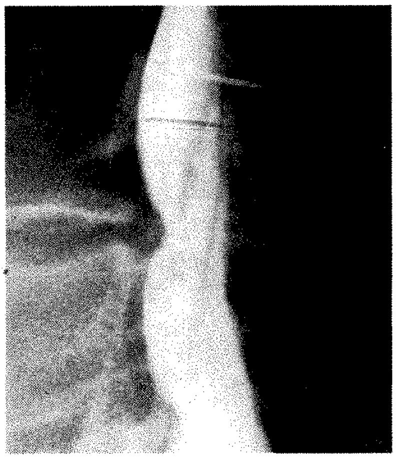

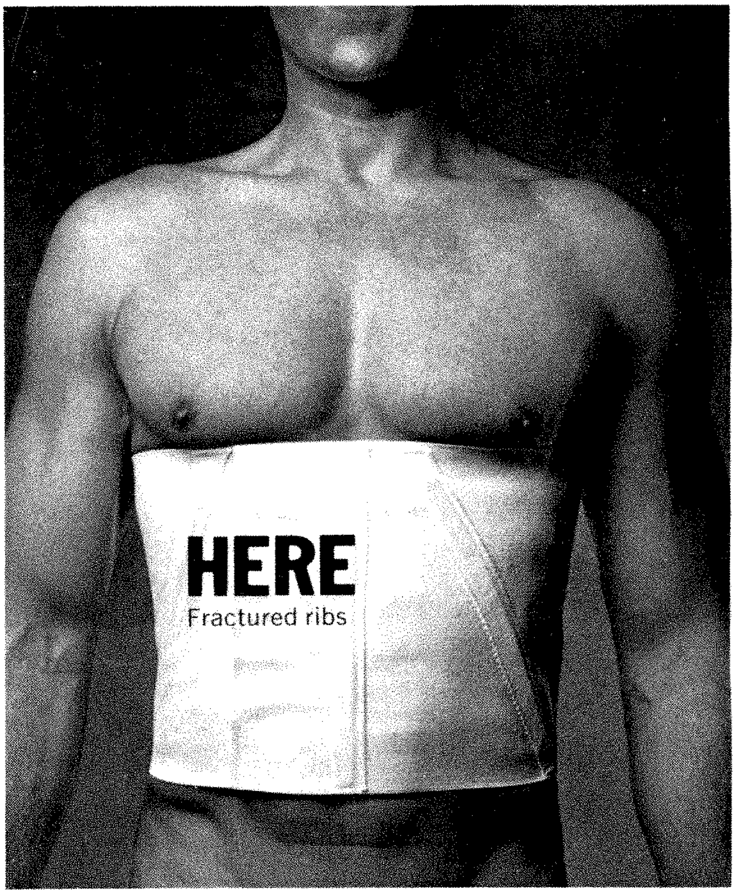

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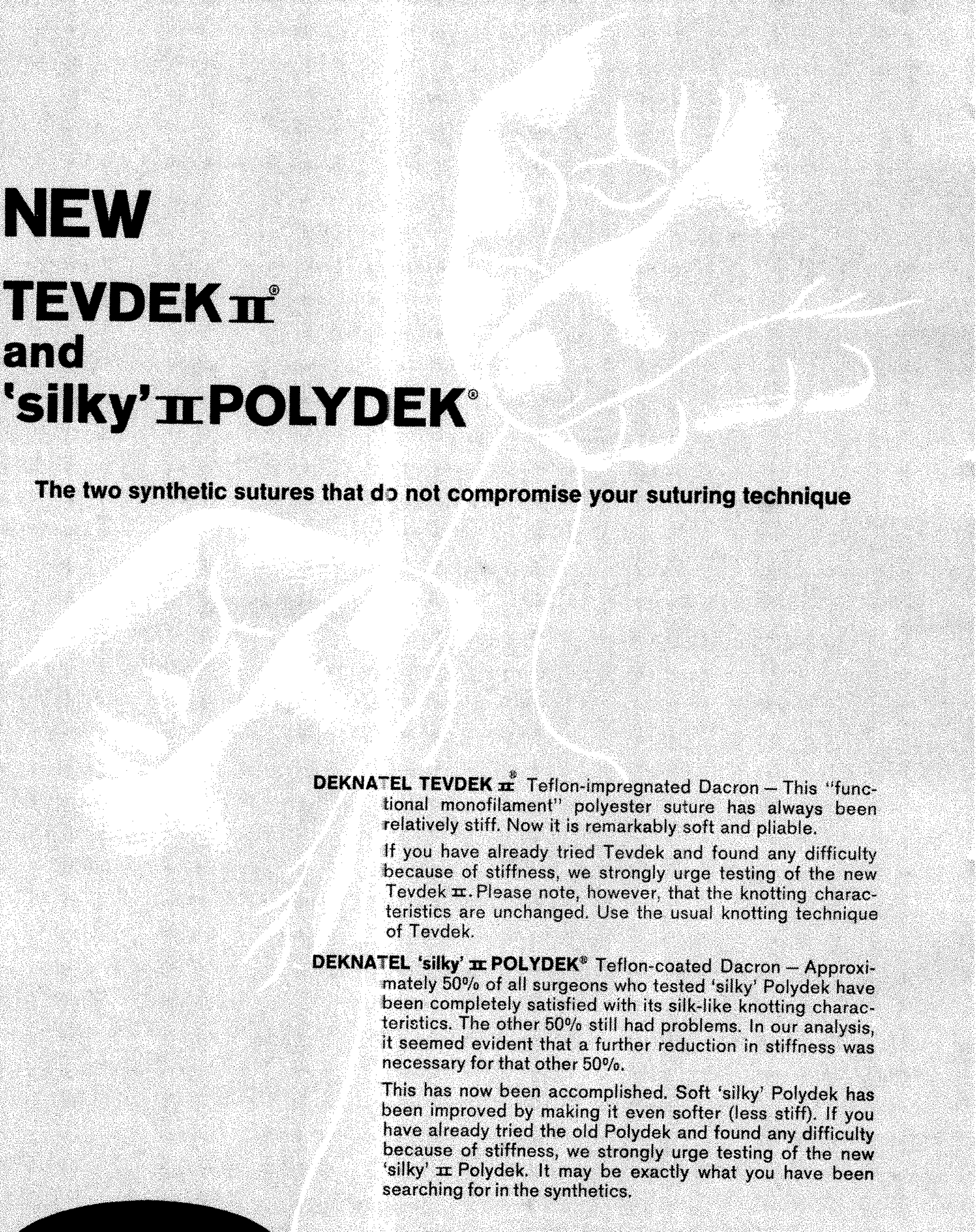

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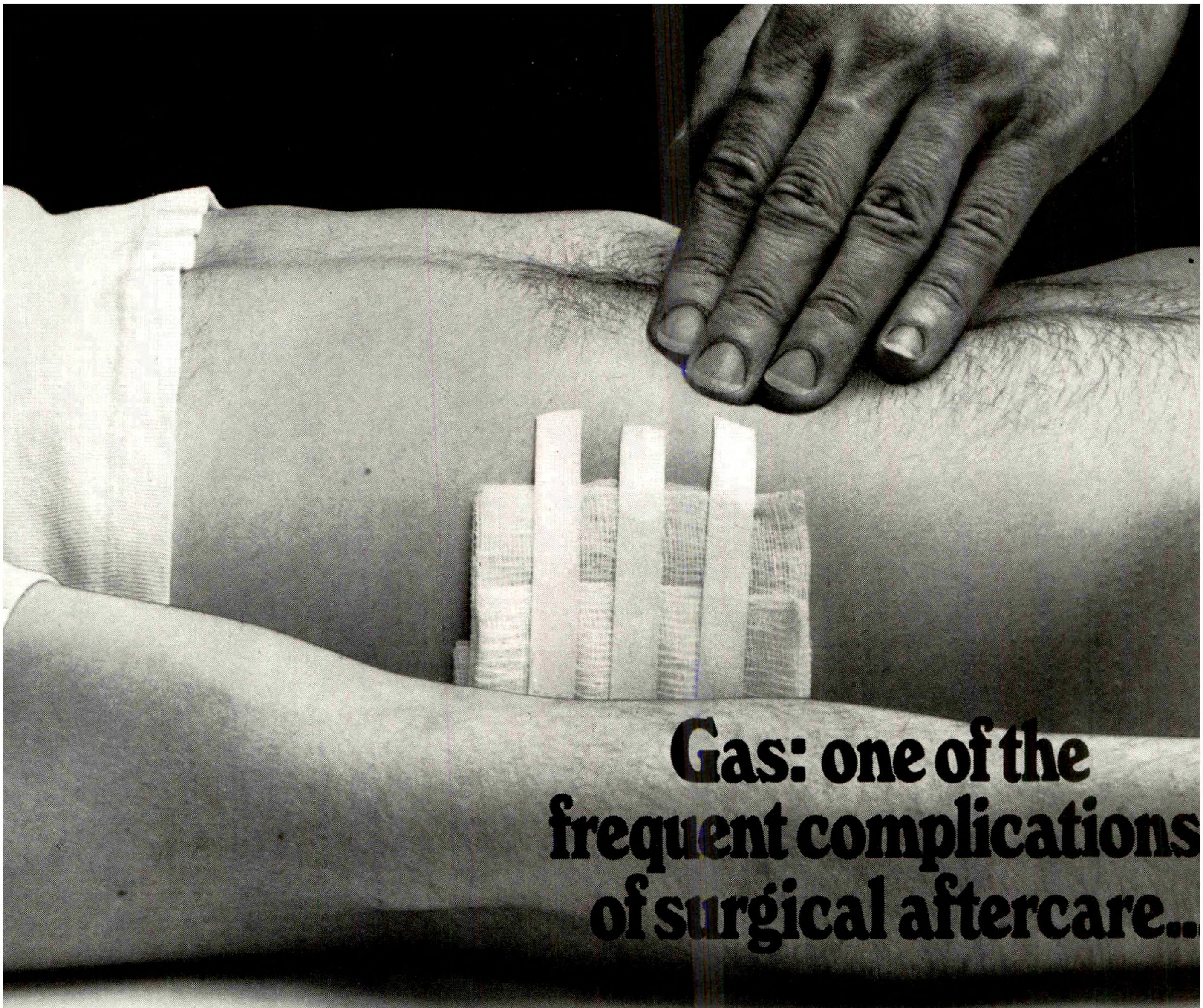

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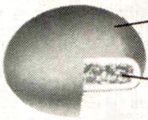

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distentio and discomfort with simethicone, *Obstet. Gynecol. 38*:386, Sept. 1971.

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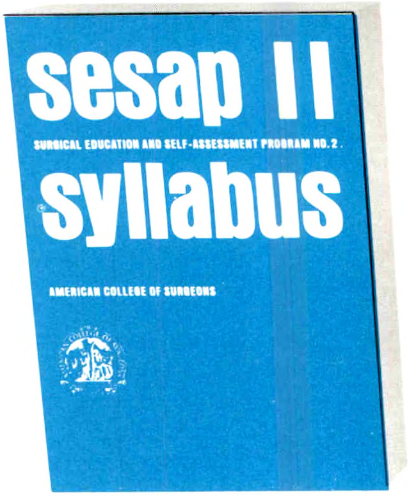
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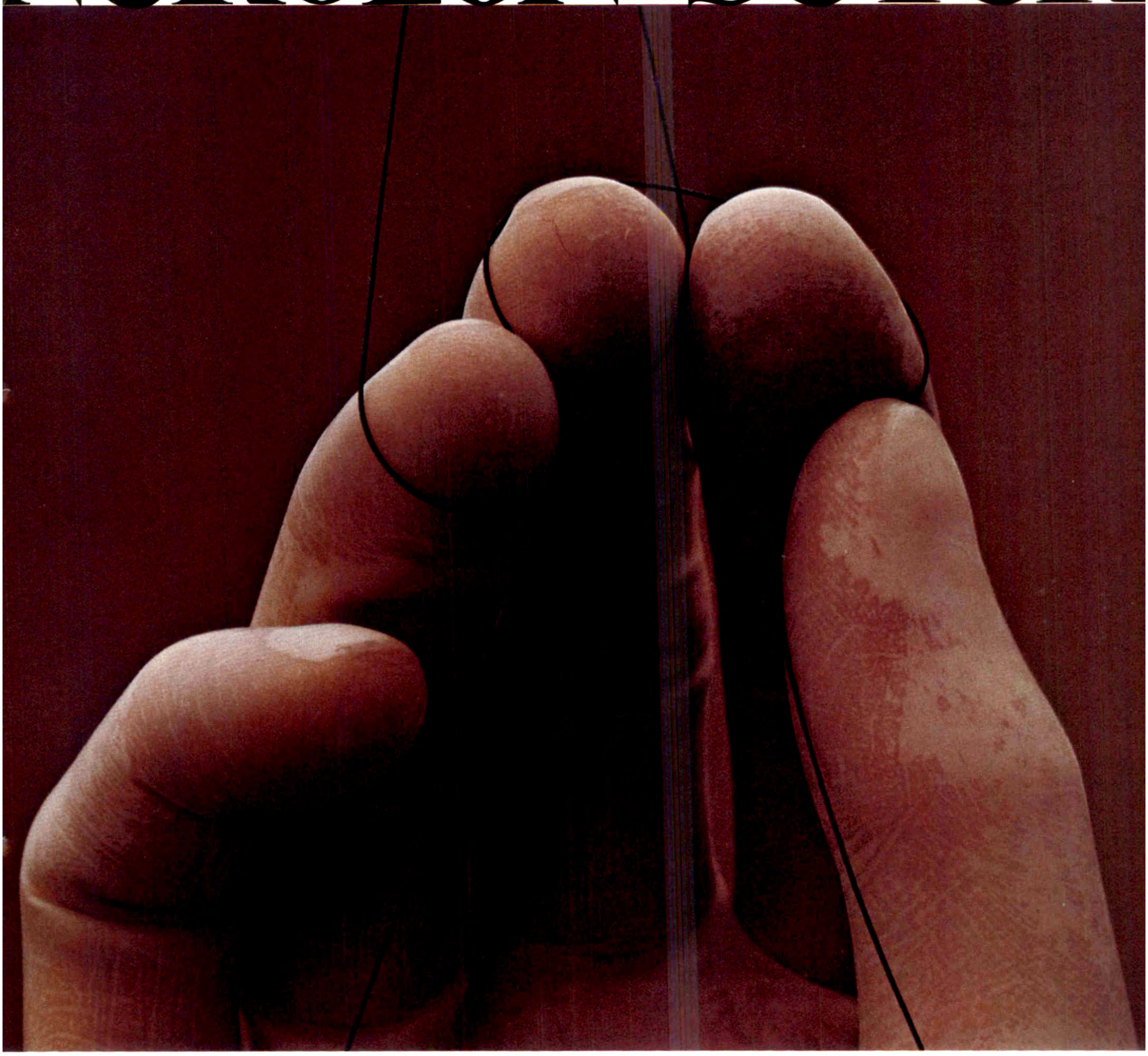

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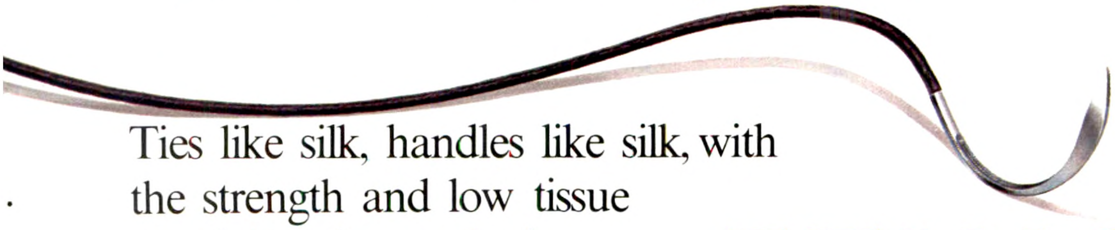

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In more than 3,000
a relatively low incidence

hen used as directed, there has been a relatively w incidence of adverse renal or eighth nerve actions with gentamicin. The risk of such actions is low in patients with normal renal nction who do not receive the drug at higher sages or for longer periods of time than commended.

A relatively low incidence of adverse renal reactions

The incidence in 3,370 cases over a period of nearly eight years is shown in the chart below. These patient case studies were derived from clinical research data and the patients were carefully monitored during the treatment period. Most of the adverse renal effects reported were of a transient nature, as demonstrated by elevated blood urea nitrogen, NPN, creatinine, and oliguria.

GARAMYCIN Injectable (gentamicin sulfate)
Incidence* of Adverse Renal Reactions

Clinical Investigation Period	1965-1966	1967-1969	1970-Oct.'73
Total Case Studies	285	1,450	1,635
Possibly Related†			
Number	18	49	23
Per Cent	6.3%	3.4%	1.4%
Probably Related			
Number	4	21	25
Per Cent	1.4%	1.4%	1.5%

*Data on file, Schering Laboratories.

†In these cases, no positive evidence exists to indicate whether GARAMYCIN Injectable precipitated the incident or if some other factor was responsible.

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY **Safety for use in pregnancy has not been established.**

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case studies...
f adverse reactions

A relatively low incidence of adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions in 3,650 cases over a period of nearly ten years is shown in the following chart. These patient case studies were derived from clinical research data and the patients were carefully monitored during the treatment period.

GARAMYCIN Injectable (gentamicin sulfate)
Incidence* of Adverse VIII Nerve Reactions

Clinical Investigation Period	1963-1966	1967-1969	1970-Oct. '73
Total Case Studies	565	1,450	1,635
Vestibular Involvement			
Only	10	18	7
With Impaired Hearing	5	3	1
Impaired Hearing	1	6	7
Total Incidence			
Number	16	27	15
Per Cent	2.8%	1.8%	0.9%

*Data on file, Schering Laboratories.

Two-thirds of these incidents of adverse eighth nerve reactions involved patients with impaired renal function. When occurring in patients with normal renal function, it is often the result of high dosage or longer duration of therapy than recommended. Cases of vestibular involvement reported to date are frequently reversible or compensated for by the patient.

Proper patient management—the key to minimizing the risk of adverse reactions

Identify the "special risk" patient. These patients include those with impaired renal function, elderly debilitated patients, and patients with deteriorating renal function due to either the infection, drug therapy, severe trauma, or major surgical procedures. These important guidelines should then be followed:

1. Follow recommended dosage schedules.
2. Monitor renal function...
   a. in patients with known or suspected renal impairment.
   b. during prolonged therapy.
3. Monitor auditory and vestibular function during prolonged therapy.
4. Adjust dosage intervals in patients with impaired renal function following serum creatinine X 8 formula.
5. Avoid concurrent use of potentially nephrotoxic or ototoxic drugs.
6. Where feasible, monitor gentamicin serum concentrations and avoid prolonged levels above 12 mcg./ml.

In serious gram-negative infections**

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gentamicin sulfate **injectable**
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** Due to susceptible organisms

See Clinical Considerations section which follows...

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> **WARNING**
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> **Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.**
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> **Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.**
>
> **GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.**
>
> **Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.**
>
> **In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.**
>
> **Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.**
>
> **Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.**
>
> **The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.**
>
> **USAGE IN PREGNANCY Safety for use in pregnancy has not been established.**

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:
Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura, fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION
GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:
*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:
The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

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For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

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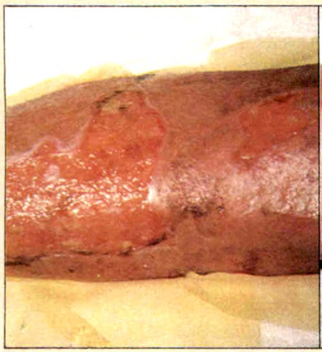

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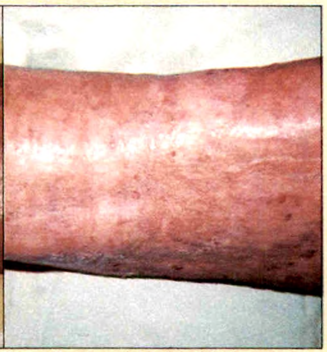

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Animal Study[2]* Using Sprague-Dawley rats, another group of investigators studied the effect of various topical dressings on donor site epithelization. They concluded: all dressings were superior to the control (exposure to air) and "Scarlet Red and Xeroform were statistically superior to all other dressings [studied] ($P < .05$)."[2]†

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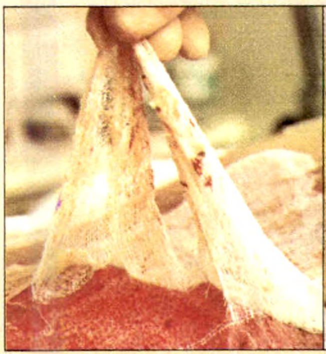

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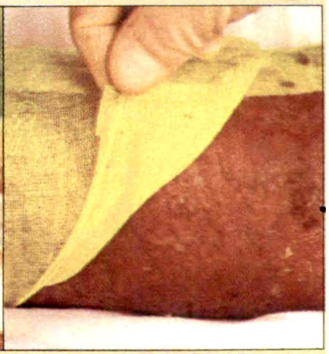

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*Animal data are not intended to imply the same effect in humans. Human studies are now under evaluation.

†Both SCARLET RED and XEROFORM are nonadhering dressings from Chesebrough-Pond's Inc.

1. Bellinger, C. G. and Conway, H.: Plast. Reconstr. Surg. *45*:582, June 1970
2. Salomon, J.C., Diegelmann, R.F. and Cohen, I.K.: Surg. Forum *25*:516, 1974

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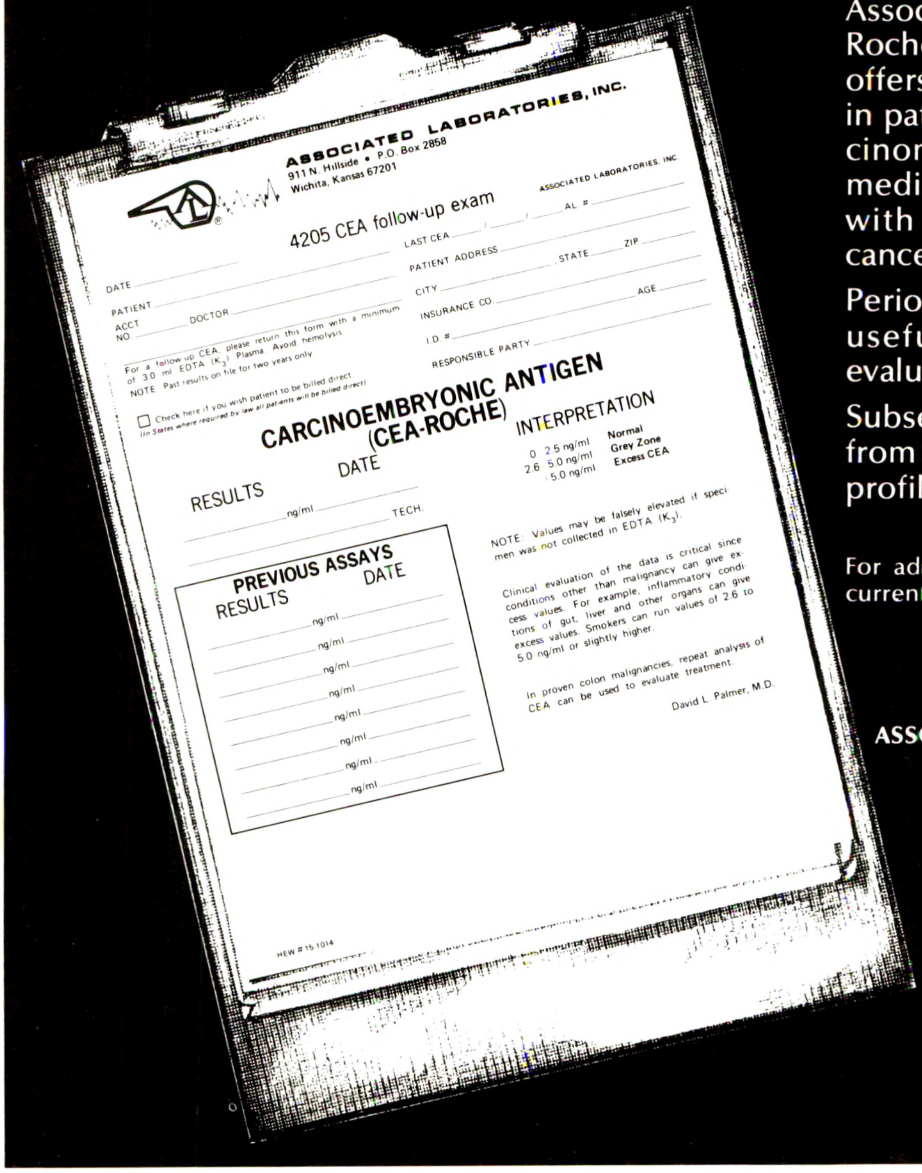

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4205 CEA follow-up exam

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RESPONSIBLE PARTY

For a follow up CEA, please return this form with a minimum of 3.0 ml EDTA (K_3) Plasma. Avoid hemolysis
NOTE: Past results on file for two years only

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(In States where required by law all patients will be billed direct)

CARCINOEMBRYONIC ANTIGEN (CEA-ROCHE)

RESULTS DATE
ng/ml TECH.

INTERPRETATION

0 - 2.5 ng/ml	**Normal**
2.6 - 5.0 ng/ml	**Grey Zone**
>5.0 ng/ml	**Excess CEA**

PREVIOUS ASSAYS

RESULTS DATE
ng/ml
ng/ml
ng/ml
ng/ml
ng/ml
ng/ml
ng/ml
ng/ml

NOTE: Values may be falsely elevated if specimen was not collected in EDTA (K_3).

Clinical evaluation of the data is critical since conditions other than malignancy can give excess values. For example, inflammatory conditions of gut, liver and other organs can give excess values. Smokers can run values of 2.6 to 5.0 ng/ml or slightly higher.

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Influence of the Postoperative State on the Intracellular Free Amino Acids in Human Muscle Tissue

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Five patients were studied before and two to three days after major, uncomplicated abdominal operation. Muscle tissue was obtained by needle biopsy from m. quadriceps femoris after eight hours overnight fast. Plasma free amino acids were analyzed in simultaneously obtained samples. In the homogenized muscle samples the intracellular concentration of each amino acid (IC) was calculated by subtracting the free extracellular part from the total amount, assuming the plasma concentration to be equal to the concentration in the interstitial fluid. Their relationships have also been calculated (IC/EC gradient). The extra- and intracellular water distribution was estimated using a modified chloride method.

In similarity to the findings in normal subjects the majority of the amino acids showed much higher concentration in intracellular water than in plasma. Preoperatively all amino acids examined in muscle biopsies were formed within normal limits. Postoperatively the total amount of free amino acids in plasma and muscle was decreased, and the amino acid profiles differed from those observed in normal subjects. In plasma, as compared with normal controls, the most significant changes were an increase in phenylalanine and tyrosine and a decrease in serine, proline, histidine and isoleucine. In muscle the greatest decrease occurred in the concentrations of glutamine, arginine and lysine followed by proline and glutamic acid. The increases in taurine, valine and phenylalanine were all highly significant and in serine, glycine, alanine and leucine significant, whereas tyrosine showed only a moderate rise. Compared with normal values there were marked increases in the gradient between intracellular and plasma concentrations which were highly significant for glycine and valine and significant for serine, alanine, isoleucine and leucine. The shift in the methionine gradient was somewhat less.

We confirm that alterations in the muscle free amino acid pool are not reflected in the values found in plasma. Further work is required to explore the clinical significance of the observed variations in individual amino acids.

A PROMINENT FEATURE of acute surgical catabolism is a negative nitrogen balance associated with protein breakdown and increased urea synthesis and excretion. Despite the repeated confirmation of these findings since first reported,[13] the underlying mechanism and physiologic significance remain obscure.

Muscle is the main cellular tissue which is broken down in conditions of increased catabolism and nitrogen

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TABLE 1.

Patient, Sex, Age	Diagnosis	Operation
A.L., F, 25	Hypoplastic Kidney	Nephroureterectomy
K.A., M, 68	Ulcus duodeni	Partial gastrectomy B II
B.O., F, 30	Myoma uteri	Total hysterectomy
S.O., F, 37	Colitis ulcerosa	Colectomy
K.M., M, 70	Ulcus duodeni c. retentio	Partial gastrectomy B I

metabolism studies of injured patients have suggested a change in cytoplasmic amino acids in muscle. However, measurements of intracellular amino acids have not been available in the past and the level of amino acids in plasma are known to be a poor indicator of both the amount and the composition of intracellular amino acids.

The amount of free amino acids is considerably greater in the cells of human muscle than in the extracellular fluid,[5] and it is not possible to draw any conclusions concerning the tissue amino acid pool by determining their concentrations in plasma. In addition, several animal investigations have shown that intracellular concentrations differ between species.[17,19,22,44] It is therefore of great importance to obtain information on free intracellular amino acids in different catabolic states and during specific nutritional treatment of catabolism. In the following paper we will report the results of studies of the free amino acid concentrations in muscle tissue, using the muscle biopsy technique[3] on 5 patients undergoing surgical operations of moderate severity without complications.

Material and Methods

Five patients were studied after routine uncomplicated operation. The age, sex, diagnosis and type of operation are shown in Table 1. All patients were eating a regular diet and were well-nourished and showed normal blood chemistry. They were in good health except for local disease requiring operation. Patient S.O. underwent colectomy for the danger of malignant change, although the disease was in a quiescent stage. The muscle biopsies were taken before the operation and on the third postoperative day, except K.M., who was biopsied on the fourth postoperative day. The clinical course and blood chemistries of each patient were entirely consistent with a normal convalescence at the time of the muscle biopsies. Venous blood was obtained for determination of plasma free amino acids, electrolytes and protein. All patients were given 2000 ml of Normodex® (Pharmacia, Uppsala, Sweden) intravenously daily. Normodex® contains per liter fructose 112, 5 g, glucose 37, 5 g, Na^+ 40 meq, K^+ 20 meq, Mg^{++} 3 meq, Ac^- 23 meq and Cl^- 40 meq. No nitrogen was administered. No oral nutrition was provided. The patients were fasting and without any infusions for 8 hours before the postoperative biopsies were taken. Preoperative biopsies were taken in every patient, however, the postabsorptive period was delayed from 8 hours to as long as 13 hours due to daily variations in the operative schedule.

The muscle samples were taken from the lateral portion of the quadriceps femoris, about 15-20 cm above the knee, after local anesthesia of the skin.[3] The nature, purpose and possible risks involved in the biopsy technique were explained to the patients before obtaining their voluntary consent.

The wet biopsy material was dissected carefully to remove visible fat and connective tissue. The material was divided into several portions. Two smaller portions (10-15 mg) were used for determination of water, fat and electrolytes. A larger amount (20-30 mg) was used for measurements of free amino acids. The methodology for weighing the samples and for the determination of neutral fat, water, chloride and free amino acids in muscle tissue and plasma has been described in detail.[5] Routine chemistries were carried out on each plasma sample, using a 20 channel Autochemist. The determination of extra- and intracellular water was based on the chloride method. Chloride is freely diffusible across the skeletal muscle fiber membrane and is distributed according to Nernst's equation.[11] Taking the resting membrane potential of muscle in normal man to be −87.2 mV,[7] the Cl_e/Cl_i ratio calculated from Nernst's equation will be 26/1; if the total water and chloride content of the muscle tissue and the extracellular concentration of chloride (obtained by correcting the plasma chloride concentration for a Donnan factor and a factor for plasma water[3] are known, extra- and intracellular water volumes can be calculated.[4,18]

The intracellular concentration of each amino acid was

TABLE 2. *Fat Content and Water Distribution in 5 Patients Pre- and Postoperatively per 100 g Dry Fat Free Solids Compared with Normal Subjects.*

	Normal Subjects			Patients			
				Preop		Postop	
	n	Mean	SE	Mean	SE	Mean	SE
Fat g	44	7.2	4.21	8.2	2.01		
H_2O_T ml	20	337	2.91	357*	7.50	344.5	9.46
H_2O_E ml	20	38	2.46	55*	7.50	62.5‡	9.83
H_2O_I ml	20	298	2.68	302	1.02	282 *	5.29

Significance test was calculated between the normal means and the respectively means obtained pre- and postoperatively using Student t test.
*P<0.05 †P<0.01 ‡P<0.001

TABLE 3. *Plasma Free Amino Acids (mmol/l Plasma) in Healthy Subjects and in 5 Patients, Pre- and Postoperatively After Overnight Fasting.*

	Normal Subjects			Patients				Significance
Non-essential Amino Acids	n	Mean	SE	n	postop Mean	SE	preop	
Taurine	21	0.07	0.005	5	0.09	0.018	(0.04 ± 0.013)	NS
Aspartate	20	0.01	0.001	3	0.01	0.003	(0.01 ± 0.002)	NS
Asparagine	20	0.05	0.002	5	0.05	0.004	(0.04 ± 0.001)	NS
Serine	21	0.12	0.004	5	0.10	0.004	(0.10 ± 0.007)	$P<0.05$
Glutamate	18	0.06	0.005	5	0.06	0.012	(0.06 ± 0.018)	NS
Glutamine	20	0.57	0.020	5	0.50	0.049	(0.55 ± 0.060)	NS
Proline	21	0.17	0.010	5	0.12	0.015	(0.14 ± 0.016)	$P<0.05$
Glycine	21	0.21	0.012	5	0.16	0.012	(0.19 ± 0.019)	NS
Alanine	21	0.33	0.021	4	0.26	0.028	(0.27 ± 0.014)	NS
Tyrosine	21	0.05	0.002	5	0.07	0.006	(0.07 ± 0.012)	$P<0.001$
Ornithine	21	0.06	0.003	5	0.05	0.014	(0.08 ± 0.010)	NS
Histidine	20	0.08	0.003	5	0.05	0.002	(0.05 ± 0.003)	$P<0.001$
Arginine	20	0.08	0.003	5	0.09	0.016	(0.09 ± 0.010)	NS
Essential Amino Acids								
Threonine	21	0.15	0.007	5	0.13	0.014	(0.11 ± 0.008)	NS
Valine	21	0.22	0.009	5	0.22	0.028	(0.17 ± 0.020)	NS
Methionine	21	0.02	0.001	5	0.02	0.003	(0.02 ± 0.001)	NS
Isoleucine	21	0.055	0.002	5	0.05	0.001	(0.04 ± 0.005)	$P<0.001$
Leucine	21	0.12	0.005	5	0.15	0.011	(0.11 ± 0.026)	$P<0.05$
Phenylalanine	21	0.05	0.001	5	0.08	0.010	(0.06 ± 0.010)	$P<0.001$
Lysine	20	0.18	0.007	5	0.15	0.012	(0.14 ± 0.008)	NS
$\frac{\text{Phenylalanine}}{\text{Tyrosine}}$	21	0.95	0.012	5	1.06	0.129	(0.90 ± 0.058)	NS

The brackets enclose the corresponding preoperative means ± SE

calculated by subtracting the free extracellular part from the total amount assuming the plasma concentration to be equal to the concentration in the interstitial fluid. The calculation of these relationships has also been described in detail.[5]

Results

Two males and three females were included in the study. The age range was 25 to 70 years.

The mean values and standard deviations of total water and fat content and the intra- and extracellular distribution of water in muscle tissue, pre- and postoperatively, are shown in Table 2 and are compared with corresponding values obtained from normal subjects from earlier work.[4] Compared with the normal means slightly increased total and extracellular water content was observed preoperatively. Significantly elevated extracellular and decreased intracellular water content was detected in the same patients 3-4 days after the operation.

The pre- and postoperative mean values (±SE) of the essential and non-essential free amino acids in plasma expressed in mmol/l plasma and in muscle tissue expressed in mmol/l intracellular water and the gradients between intracellular muscle and plasma water concentrations are shown in Tables 3-5. These means are compared with corresponding values obtained from normal subjects from our earlier work[5] (see discussion).

The preoperative means for intracellular muscle free amino acids did not deviate significantly from the mean values obtained in normal control subjects. However, changes in plasma values of certain amino acids were observed at the time of the preoperative biopsies which would influence the gradient between plasma and muscle cells.

In posttraumatic plasma, as compared with normal controls, the most significant changes ($P<0.001$) were an increase in phenylalanine and tyrosine and a decrease in isoleucine and histidine (Table 3). Serine and proline showed more moderate decreases while leucine increased slightly ($P<0.05$). The decreases in glycine, alanine and lysine were not significant.

In muscle, as shown in Table 4, the greatest decrease occurred in the concentrations of glutamine, arginine, and lysine ($P<0.01$) followed by proline and glutamic acid ($P<0.05$). The increase in taurine, valine and phenylalanine were all highly significant ($P<0.001$) and in serine, glycine, alanine and leucine significant ($P<0.01$) whereas tyrosine and citrulline showed only a moderate rise ($P<0.05$).

Compared with normal values there were marked increases in the gradients between intracellular and plasma concentrations which were highly significant for glycine and valine ($P<0.001$) and significant for serine, alanine, isoleucine and leucine ($P<0.01$). The shift in the methionine gradient was somewhat less ($P<0.05$) while the other amino acid gradients showed insignificant variations from the normal pattern.

The phenylalanine/tyrosine ratio was increased in both

TABLE 4. *Muscle Free Amino Acids (mmol/l intracellular water) in Healthy Subjects and in 5 Patients, Pre- and Postoperatively After Overnight Fasting.*

	Normal Subjects			Patients				Significance
				postop			preop	
Non-essential Amino Acids	n	Mean	SE	n	Mean	SE		
Taurine	16	15.44	0.695	5	22.45	1.775	(15.04 ± 1.270)	P<0.001
Aspartate				3	1.21	0.024	(1.21 ± 0.150)	
Asparagine	8	0.47	0.035	5	0.75	0.191	(0.44 ± 0.118)	NS
Serine	18	0.98	0.044	5	1.34	0.164	(0.91 ± 0.138)	P<0.01
Glutamate	14	4.38	0.164	5	3.40	0.614	(4.07 ± 0.410)	P<0.05
Glutamine	9	19.45	0.508	5	12.09	2.271	(18.62 ± 0.161)	P<0.01
Proline	17	0.83	0.048	5	0.61	0.048	(0.68 ± 0.043)	P<0.05
Glycine	18	1.33	0.087	5	1.96	0.230	(1.33 ± 0.238)	P<0.01
Alanine	18	2.34	0.109	5	3.04	0.114	(2.03 ± 0.301)	P<0.01
Citrulline	12	0.04	0.011	5	0.13	0.058	(0.04 ± 0.011)	P<0.05
Tyrosine	14	0.10	0.007	5	0.13	0.012	(0.10 ± 0.015)	P<0.05
Ornithine	9	0.30	0.053	5	0.22	0.031	(0.29 ± 0.077)	NS
Histidine	11	0.37	0.044	5	0.26	0.044	(0.26 ± 0.013)	NS
Carnosine	6	4.47	0.396	5	5.05	1.340	(3.43 ± 0.584)	NS
Arginine	18	0.57	0.046	5	0.30	0.037	(0.71 ± 0.042)	P<0.01
Essential Amino Acids								
Threonine	17	1.03	0.044	5	1.10	0.061	(0.65 ± 0.045)	NS
Valine	18	0.26	0.024	5	0.50	0.071	(0.29 ± 0.064)	P<0.001
Methionine	11	0.05	0.008	5	0.11	0.027	(0.09 ± 0.021)	NS
Isoleucine	14	0.11	0.024	5	0.20	0.046	(0.11 ± 0.047)	NS
Leucine	13	0.15	0.021	5	0.32	0.048	(0.14 ± 0.028)	P<0.01
Phenylalanine	14	0.07	0.006	5	0.14	0.011	(0.07 ± 0.011)	P<0.001
Lysine	13	1.15	0.077	5	0.67	0.061	(0.89 ± 0.089)	P<0.01
Phenylalanine / Tyrosine	14	0.72	0.025	5	1.10	0.103	(0.74 ± 0.155)	P<0.001

The brackets enclose the corresponding preoperative means ± SE

plasma and muscle compared with normal values (Tables 3 and 4), however, this increased ratio was only significant in muscle ($P<0.001$).

Discussion

In any investigation which uses a small tissue sample technique it is essential that the investigated substances be distributed uniformly throughout the tissue. In a study of muscle glycogen content in normals, no differences were found at different levels of the quadriceps femoris.[24] Likewise, no differences could be shown in duplicate biopsy specimens for energy-rich phosphates or for lactate.[21,28] Muscle sodium, potassium, magnesium and chloride showed no differences in similar unpublished studies from our laboratory. However, comparative studies of different muscle groups in the same subject demonstrated variations in several substances such as glycogen, sodium, potassium and magnesium.[16,24] These observations stress the importance of using the same muscle group for comparative studies. In the present investigation tissue samples were obtained solely from the quadriceps femoris using a needle biopsy technique with local anesthesia being confined to the skin.[3]

For the calculation of the concentrations of individual amino acids in the intracellular water the chloride method was employed. Chloride is passively distributed across the resting muscle fiber membrane according to Nernst's equation[11,41] and knowledge of the membrane potential permits the determination of extra- and intracellular water content. In the present investigation we assumed a normal membrane potential of −87.2 mV.[7] However, under certain clinical and experimental conditions such as experimental anuria and congestive cardiac failure increasing amounts of chloride may enter the cells.[15,20,34] A constant and sustained fall in membrane potential has been demonstrated during acute hemorrhagic shock in rats and dogs.[10,36] Cunningham et al.[12] also found a decreased membrane potential in severely ill subjects but normal potentials in patients who were mildly ill.

In the present investigation none of the patients had renal failure or was in shock nor were there any postoperative complications. There was, therefore, no reason to believe that membrane potentials should have been influenced by surgery in any of our patients. Furthermore, individual deviations of ±10 mV would not have influenced the estimated intracellular water content by more than 2%.[5] This is negligible in comparison with the errors inherent in the determination of the individual amino acids which ranges from 2.8% to 9.1%.

Initially, we attempted to use the preoperative values for comparison with the postoperative state, consequently using the patients as their own controls. However, the preoperative biopsies could not be obtained at exactly the same postabsorptive interval as the postoperative biopsies, due to variations in the operative schedule. Three of our 5

TABLE 5. *Gradient Between Intracellular and Plasma Water Concentration in mmol/l of Free Amino Acids in Healthy Subjects and in 5 Patients, Pre- and Postoperatively After Overnight Fasting.*

	Normal Subjects			Patients				Significance
				postop			preop	
Non-essential Amino Acids	n	Mean	SE	n	Mean	SE		
Taurine	16	220.4	21.34	5	234.0	26.98	(440.7 ± 111.22)	NS
Aspartate				3	144.3	34.97	(154.3 ± 26.36)	
Asparagine	8	9.5	1.06	5	14.8	2.89	(12.4 ± 1.80)	NS
Serine	18	6.9	0.69	5	12.0	0.95	(8.9 ± 1.26)	P<0.01
Glutamate	14	73.2	9.16	5	60.6	8.31	(62.6 ± 10.40)	NS
Glutamine	9	33.8	3.91	5	23.2	2.88	(35.3 ± 5.24)	NS
Proline	17	4.9	0.34	5	5.2	0.66	(5.0 ± 0.81)	NS
Glycine	18	6.6	0.53	5	12.5	2.05	(8.1 ± 2.60)	P<0.001
Alanime	18	7.3	0.61	4	12.0	2.03	(8.4 ± 4.75)	P<0.01
Tyrosine	14	2.0	0.21	5	1.8	0.25	(1.6 ± 0.24)	NS
Ornithine	9	5.1	0.53	5	3.9	0.91	(4.1 ± 1.47)	NS
Histidine	11	4.6	0.51	5	5.0	0.88	(4.8 ± 0.89)	NS
Arginine	18	6.4	0.79	5	3.4	0.60	(8.0 ± 1.36)	NS
Essential Amino Acids								
Threonine	17	6.8	0.61	5	9.1	0.90	(6.0 ± 0.28)	NS
Valine	18	1.2	0.10	5	2.3	0.34	(1.7 ± 0.25)	P<0.001
Methionine	15	5.6	0.48	5	8.3	1.77	(3.5 ± 1.19)	P<0.05
Isoleucine	14	1.8	0.21	5	3.0	0.34	(3.7 ± 1.61)	P<0.01
Leucine	14	1.2	0.14	5	2.3	0.29	(1.3 ± 0.12)	P<0.01
Phenylalanine	14	1.2	0.18	5	1.9	0.25	(1.5 ± 0.20)	NS
Lysine	13	6.4	0.58	5	4.6	0.53	(7.0 ± 0.71)	NS

The brackets enclose the corresponding preoperative means ± SE

patients were fasting up to 13 hours before the preoperative biopsies were taken. In these patients some of the plasma amino acid concentrations showed changes from the normal mean values. These changes probably may be due to the delayed postabsorptive period, as it has been shown that the concentration of plasma amino acids vary significantly during the day, depending upon dietary conditions.[25] The postoperative biopsies, however, were taken during the same conditions as our previously reported normal material, making these two series comparable. Accordingly, we considered it more reliable to compare the obtained postoperative results with our recently published normal material,[5] despite the fact that normal preoperative muscle values were obtained in these patients. These results also indicate that the amino acid profiles, preoperatively, were not influenced by the disease state.

The preoperative value for extracellular water content was slightly higher than previously reported values for healthy young subjects.[4] This difference may be associated with the older average age and uncertain previous nutrition of these patients. The current study showed the chloride and extracellular water content to be markedly increased and the intracellular water content to be slightly decreased compared with normal subjects. The increase in extracellular water content is consistent with the known fact that surgical trauma results in sodium and water retention.[32,36] The observed slight decrease in intracellular water content could either represent true intracellular dehydration or be an artefact which ensues because of chloride shift into the cells, an aspect which was not taken into consideration in our calculations.

Independently from these methodological considerations a number of physiological determinants of muscle metabolism must be considered, such as the influence of sex and age, the influence of endocrine factors and the effect of starvation. A lower level of some of the plasma amino acids has been reported in adult women as compared with men.[30] The present investigation contained too few patients to evaluate this factor. Variations have also been shown for different age groups.[33] In preliminary unpublished studies we have determined the intracellular free amino acid and electrolyte concentrations and water distribution in four elderly, well-nourished men in the ages of 75-85. Surprisingly, these values were all in the normal ranges compared with our younger subjects.[5] The results are important because two of our patients were 68 and 70 years old, showing normal preoperative values. The postoperative differences we were able to demonstrate, therefore, seem to be independent of sex and age.

Trauma or surgery initiate a change in endocrine balance. From the metabolic point of view the increase in corticosteroid levels in plasma is the most interesting. Corticosteroids are generally thought to increase the levels of most free amino acids in muscle in the mouse and in the rat.[6,27,35]

This effect seems to be due to inhibition of muscle protein synthesis.[43] Although the corticosteroid effect is of importance it does not seem that our results can be explained by this alone since increases as well as decreases in the intracellular concentration of individual free amino acids were observed.

Insulin causes a rapid reduction in the plasma levels of amino acids[33] whereas in muscle it leads to an increase of six amino acids while 13 others remain unchanged.[42] Carbohydrate infusions have a similar effect.[33] In order to avoid these hormonal or nutritional effects in our investigation, test samples were taken after 8 hours of fasting.

By supporting our patients with 300 g of carbohydrates daily, up to 8 hours before their biopsy, basic non-protein energy requirements were supplied according to Kinney.[29] Therefore, results are not expected to have been influenced by caloric deficiencies. By supplying electrolytes we tried to avoid a deficiency especially of potassium which is known to raise the levels of lysine, arginine and histidine in skeletal muscle of rats.[8,26,31]

In all species, except lamb, prolonged fasting (4-6 weeks) causes an increase in the plasma levels of cystine and the branch-chained amino acids with a concommitant drop in threonine concentration; other amino acids remain unchanged.[33] With longer periods of starvation the branch-chained amino acids later decreased.[1,14,38,39] Phenylalanine and lysine were much less affected, whereas glycine, alanine, proline, histidine, serine and aspartic acid were found to be well maintained or even increased.[40]

In a separate preliminary study we have investigated in man the pattern of the intracellular free amino acids after one and four days of total starvation, respectively. After 4 days of starvation the branch-chained amino acids were increased but threonine, lysine, phenylalanine and tyrosine were decreased. These findings are not in agreement with the current results during the postoperative catabolic state where threonine was unchanged and phenylalanine increased. The most pronounced differences between the two studies, however, concerned the changes in glutamine and glutamate. Glutamine which was greatly decreased after surgery had remained normal after 4 days of starvation. Glutamate, on the other hand, which showed a small decrease after surgery had been reduced much more after starvation. These observations indicate that our current results cannot be explained by protein starvation alone.

In the postoperative catabolic state the total amount of the recovered essential amino acids listed in the tables was practically unchanged in comparison with normal controls, both in plasma (0.80 mmol/l ECV in normals vs. 0.80 mmol/l ECV post surgery) and in muscle (2.88 mmol/l ICV in normals vs. 3.15 mmol/l ICV post surgery). There were, however, marked differences in individual amino acids. The branch-chained amino acids were essentially unchanged with the exception of isoleucine, which was significantly decreased in plasma and leucine slightly increased. Lysine showed a slight decline while phenylalanine was greatly increased. In muscle phenylalanine and the branch-chained amino acids, with the exception of isoleucine, were significantly increased, whereas lysine levels dropped markedly.

In comparison with normal values the level of total non-essential amino acids, excluding taurine, fell both in plasma and in muscle. In muscle the dramatic fall in glutamine levels was almost compensated by a comensurate rise in taurine. Arginine and proline were lowered to a lesser extent whereas serine, glycine and alanine rose. In plasma the serine, histidine and proline values showed a sharp decline. These observations are in agreement with Shreier and Karsh[37] who also observed a fall in the plasma levels of a number of amino acids, excepting leucine and isoleucine.

As we earlier reported,[5] the total determined free amino acid concentration was found to be about 35 mmol/l intracellular water. This concentration corresponded in a "normal man," calculated on a 40% muscle mass, to a total intracellular muscle pool of about 86 g amino acids. Contrary to earlier hypothesis, which suggest increased free amino acid pool in trauma, we found a decreased total pool in muscle compared to the normal pool size. The reduction corresponds to about 14 g amino acids or 16% of the normal pool.

During turnover studies with the aid of a deep vein catheterization, Cahill et al.[9] were able to show that alanine and glutamine were the main two amino acids derived from muscle metabolism in both the postabsorptive period as well as in starvation. In our experiments an increased alanine concentration in muscle was accompanied by a marked decrease in glutamine concentration, not a rise as one might have expected from Cahill's findings. However, as flow studies were not part of our study it is not possible to calculate turnover rates for alanine and glutamine.

It is important to note that the essential amino acid lysine which is fairly well maintained after total starvation is decreased in the postoperative state. This relative deficiency might be a limiting factor for protein synthesis by muscle tissue following surgery or trauma.

The increased phenylalanine levels in both plasma and muscle and increased phenylalanine/tyrosine ratio (Tables 3 and 4) has been thought to constitute a sign of catabolism in children with kwashiorkor and malnutrition.[2,23] Our results would indicate that this phenomenon also applies to catabolism following surgery or trauma.

Conclusions

Our studies in 5 postsurgical patients revealed marked changes in the free amino acid patterns in both plasma and muscle tissue. The amino acid profiles are different from those observed following starvation and as in earlier studies we confirmed that alterations in the muscle free amino acid pool are not reflected in the values found in plasma. Further work is required to explore the clinical significance of the observed variations in individual amino acids but now, that characteristic profiles have been defined for trauma and starvation, there is hope that each condition may be managed more effectively and in a more specific and rational manner.

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An Uncontrolled Comparison of Treatments For Achalasia

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A series of 78 patients with achalasia, seen during a 10-year period, was like those reported by others with regard to age at onset, nature of symptoms, and duration of symptoms. Analysis of the results of 5 different treatment modalities administered allows an uncontrolled comparison heretofore not available from an institution at which no one treatment was favored over all others. Those who were not treated or who received only anticholinergic medication did not become asymptomatic. Those treated by single or repeated bougienage were not improved for more than a few weeks and suffered a 6% incidence of esophageal perforation. Forty-six per cent of those treated by a single pneumatic dilatation were asymptomatic for 1 year or more. Although esophagocardiomyotomy provided symptomatic relief for 1 year or more in 85%, there was a 25% incidence of gastroesophageal reflux.

NO STUDY of the treatments for achalasia with randomization of patients among treatments has appeared, nor is this such a study. At this hospital, however, patients with achalasia may come to any of four different clinical units, each of which tends to arrive independently at diagnostic and therapeutic decisions, so that 5 different methods of management have been used. These may be considered to have been randomly applied, insofar as the physician and unit involved are determined by referral patterns or other factors probably unrelated to the severity, duration or any other aspect of the disorder.

In this review of 10 years' experience at this hospital, three patients went untreated, 7 were initially treated by medication only, 32 were dilated with mercury-filled bougies, 48 were dilated by pneumatic dilatation, and 24 had esophagocardiomyotomy. Study of this series allows comparison of the relative incidences of symptomatic relief and therapeutic complications among these methods.

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Methods and Materials

We reviewed the charts of all patients with achalasia seen at the University of Iowa Hospitals during the decade from January, 1963 through December, 1972. A radiographic study showing esophageal dilatation and disordered peristalsis proximal to a smoothly tapering, narrowed terminal esophageal segment was accepted as evidence of achalasia. Although not required, esophagoscopy was usually performed to eliminate a benign stricture or malignant obstruction at the cardia as a cause of the radiographic abnormality. The history of a vagotomy before the onset of symptoms was cause for exclusion from this study to eliminate those rare cases of "postvagotomy achalasia." For comparison with groups studied by others, the sex of the patients, the age at the time of onset, the type of symptoms, and the duration of symptoms before diagnosis were noted. In each patient, the sequence of treatment modalities and the response to therapy were recorded. From the information available patients were classified symptomatically as asymptomatic, improved, or unimproved for each treatment they were given. For a treatment regimen to be defined as successful, we required an asymptomatic interval of at least one year following its initiation. Because some patients were lost to followup, we sent detailed questionnaires to all patients for information regarding current symptomatic status. Sixty per cent of these questionnaires were answered and this information was used for the classification of response to the last treatment given.

Patient Data

Demographic Data. Seventy-eight patients met the criteria for inclusion in this review. Forty-three (55%)

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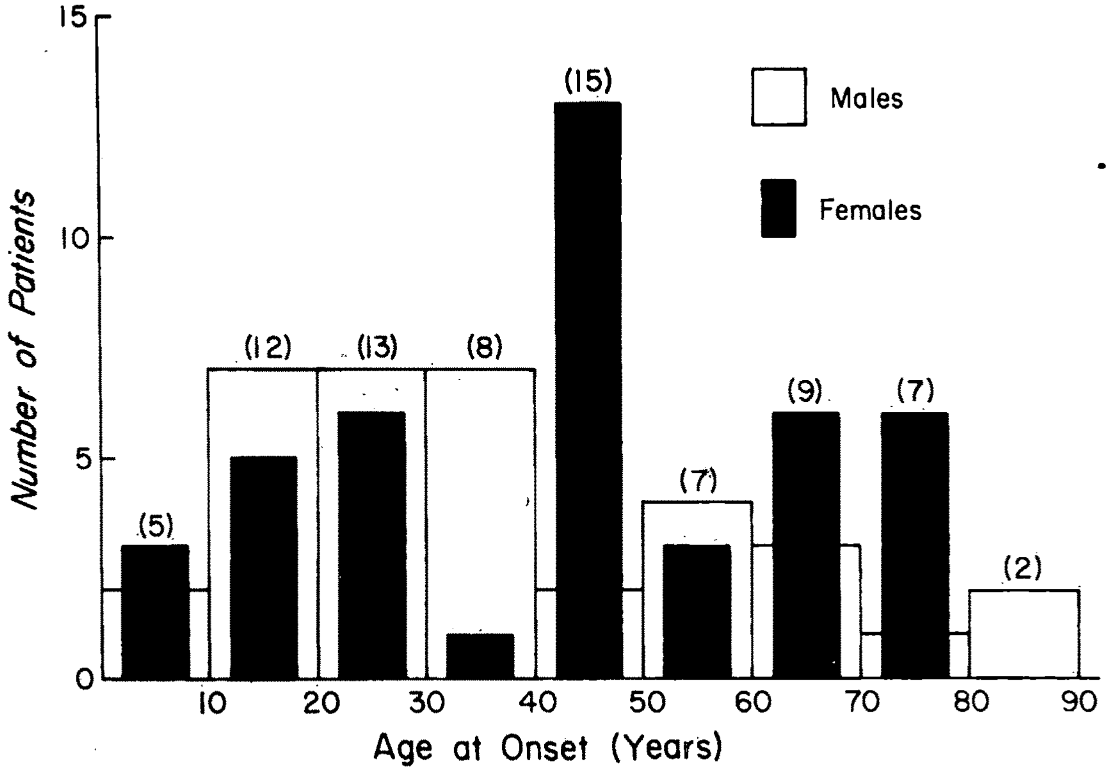

FIG. 1. The ages at onset of symptoms of achalasia in 78 patients is nearly uniformly distributed. Nearly two-thirds of the males, however, had the onset of symptoms before age 40 while a similar ratio of females experienced the first symptoms after that age.

were female (a sex preponderance which has been noted by others).[5,7,11] The ages at onset of symptoms were nearly uniformly distributed and ranged from 15 months to 82 years. Nearly half the patients experienced symptoms before age 40 (Fig. 1). Almost two-thirds of the males had the onset of symptoms before age 40, while a similar proportion of females became symptomatic after that age.

Symptoms and Signs. Sixty-four patients (82%) complained of dysphagia, usually most notable with solid food and usually described as a sense of food "hanging-up" in the lower retrosternal region (Fig. 2). A few localized the dysphagia to the neck, upper retrosternal region, or epigastrium. Dysphagia was as often associated with hot food as with cold food. Regurgitation was reported by 60 patients (77%). Weight loss of greater than 10 pounds (4.5 kg) was mentioned by 37 patients (47%). Symptoms of aspiration (e.g. choking or coughing spells) or a history of pneumonia or lung abscess was recorded for 31 patients (41%). Twenty-one patients (28%) experienced neck, chest, shoulder, back, or epigastric pain, not always associated with swallowing. One patient reported an episode of hematemesis, melena, and syncope. This was not attributable to any other disease process.

Forty-four per cent had symptoms for 1 year or less before the diagnosis was established, but nearly one-fourth had endured symptoms for 10 years or longer (Table 1).

Sixty-eight patients had esophagoscopy and 27 had esophageal manometry to confirm the diagnosis. Endoscopic study revealed little or no distal esophageal mucosal erythema in all but two cases. One of these two patients had a 40-year history of symptoms and a previous cardioplasty; an ulcerated carcinoma was found in the mid-esophagus. The second patient had a small

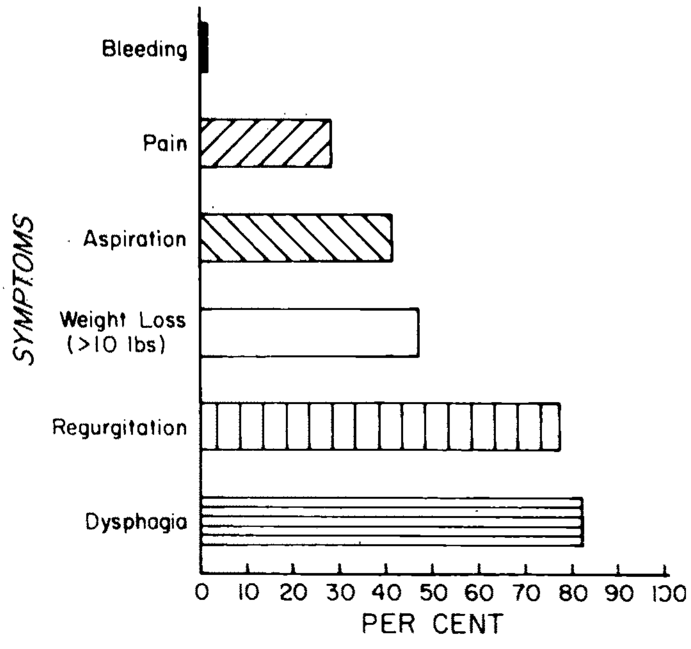

FIG. 2. The percentage of 78 patients who presented with various symptoms of achalasia is shown. Over half complained of both regurgitation and dysphagia.

TABLE 1. *Duration of Symptoms at Time of Diagnosis in 78 Patients With Achalasia*

Duration of Symptoms (Years)	Per Cent of 78 Patients
0-1	44
1-4	21
4-7	6
7-10	6
>10	23

mucosal ulceration in the distal esophagus. It was benign, and it healed after sedative and anticholinergic treatment.

In the 27 patients who underwent esophageal manometry by the infusion method, the manometric patterns were similar to those reported by others.[3,4,8]

Results

Three of the 78 patients reviewed were not treated (Table 2). One died from thyroid cancer a month after admission, and the other two did not return for treatment. Judging by his response to the questionnaire, one of these has remained symptomatic. The other remains lost to followup. Thus, no spontaneous remissions were detected.

Six of the 7 patients who were treated with anticholinergics (and occasionally with a tranquilizer) failed to improve. The one who improved became asymptomatic for 1 year and then was lost to followup. The other 6 patients in this group required further treatment (Table 2). Thus, one of 7 (14%) was successfully treated with medication alone.

There were 23 patients treated in the hospital by dilatation with mercury-filled bougies (usually to a 60 French), at least 7 of whom underwent two courses. Those patients who had such dilatation only to facilitate passage of the pneumatic dilator are not included in this analysis. Of these 23 patients, 9 were lost to followup and 14 experienced some relief of symptoms but in no case for longer than 4 months (Table 2). Two patients suffered perforation of the esophagus, and both recovered with conservative treatment. Ten of the patients in this study were instructed in periodic self-dilatation by the mercury-filled bougies. One of these 10 patients was treated unsuccessfully by bougienage in the hospital previously. Three such patients were not seen again. The other 7 experienced improvement in their symptoms for a few days to a few weeks following each dilatation. Considering both home and hospital-administered bougienage, no patient was successfully treated in this way. All patients who have been followed have required repeated dilatations or the use of a different mode of therapy to alleviate symptoms. The incidence of esophageal perforation in this combined group of 32 patients was approximately 6%.

Forty-eight patients were treated with pneumatic bag dilatation. The pneumatic bag was usually inflated to a pressure of 10 to 13 pounds per square inch for two minutes while observing its configuration and location under fluoroscopy. Four patients were lost to followup soon after dilatation and another patient died a month later of breast cancer. Nineteen became asymptomatic for a year or more following the initial dilatation (Table 2). Thus, this treatment was successful in 19 (46%) of the

TABLE 2. *Results of Treatment in 78 Patients with Achalasia*

Treatment	Number Treated	Per Cent (Number of Patients) Successfully Treated*	Number of Late Failures†	Complications (Number of Patients)
No treatment	3	0	-	-
Anti-cholinergic medication	7	14% (1)	-	-
Dilatation by mercury-filled bougie	32	0	-	Esophageal perforation (2)
First dilatation by pneumatic bag	48	46% (19)	2	Aspiration pneumonia (2) Reflux esophagitis (3)
Second dilatation by pneumatic bag	9	38% (3)	3	-
Esophago-cardio-myotomy	24	85% (17)	2	Reflux esophagitis (5) Pneumonia (2) Empyema (1)

*Success is defined as an asymptomatic period of at least 1 year following institution of a method of treatment. Per cent success is therefore based on those patients who were followed for at least 1 year.

†A late failure is defined as the recurrence of symptoms after an asymptomatic period of 1 year or more.

41 patients who were followed a year or more after the first dilatation. Two of these 19 subsequently developed a recurrence of symptoms two and a half and 4 years after their initial dilatation. This leaves 41% who were asymptomatic at the last followup, ranging from 1 year to 44 years. Eleven other patients became asymptomatic after pneumatic dilatation but did not return for yearly followup (2 patients) or developed recurrent symptoms within a year (9 patients). Six of the 48 experienced some improvement after a pneumatic bag dilatation but 9 were unchanged. Neither sex, duration of symptoms nor age seemed to influence the results of treatment.

No patient developed esophageal perforation after pneumatic dilatation, but aspiration pneumonia occurred in two immediately after treatment. Three patients developed radiographic or endoscopic evidence of gastroesophageal reflux 3 months to 6 years after dilatation. Thus, approximately 7% of the 41 patients who were followed developed gastroesophageal reflux.

Nine of this group, only two of whom had become asymptomatic for a year or more after the first pneumatic dilatation, had a second trial of pneumatic dilatation. One of the 9 was lost to followup. Of the remaining 8 patients, 3 were not improved, 2 were moderately improved, and 3 were asymptomatic following this treatment. The 3 who became asymptomatic remained so for approximately one and a half years, a success rate of about 38%. All, however, became symptomatic after one and a half years, so the success rate to the time of last followup is zero. No complications from therapy occurred in this group.

The esophagocardiomyotomy as performed at this institution consisted of a single longitudinal incision along the esophagus extending from the inferior pulmonary vein (in most instances) through the region of the lower esophageal sphincter and onto the stomach for a distance ranging from a few millimeters to 6 centimeters. A thoracic approach was used approximately twice as often as an abdominal one. An attempt was made in every myotomy to strip the mucosa from the underlying muscle over half the circumference of the esophagus. The numbers of patients who had a short or a long extension of the incision onto the stomach are too small to make any generalizations regarding later development of gastroesophageal reflux.

Twenty-four patients were treated by esophagocardiomyotomy, 11 of whom had had at least one previous pneumatic dilatation. One patient was not seen again. Three became asymptomatic after the operation but did not return for a year or more. Of the 20 patients followed a year or more after operation, 17 were asymptomatic, a success rate of 85% (Table 2). Two of the 17 (both having undergone previous pneumatic dilatation) became symptomatic again one and a half and 3 years after the esophagocardiomyotomy. Three patients were moderately improved postoperatively. One of these three had an esophagocardiomyotomy with cardioplasty. It is not known if this patient's postoperative symptoms represented reflux esophagitis or achalasia. None of the patients who underwent an esophagomyotomy was unimproved. Six patients had a fundoplication either with or after the esophagocardiomyotomy, and all have remained asymptomatic for 2 to 4 years.

Five of the 20 patients seen in followup have gastroesophageal reflux by radiographic criteria, an incidence of 25%. Two of these 5 developed severe esophagitis. Two patients developed pneumonia and one an empyema postoperatively. One patient returned a year after operation with an acute herniation of the stomach into the thorax.

Discussion

In general, this group of patients resembles those reported by others with respect to preponderance of females, age of onset of symptoms, and types and duration of symptoms before treatment.[5,7,11] To our knowledge, however, the observation from this series that approximately two-thirds of the females had the onset of symptoms after age 40 while a similar ratio of males developed symptoms before age 40, has not been made previously. This may represent a sampling error, for in a larger series from the Mayo Clinic no such observation was made.[10]

Two patients developed mid-esophageal epidermoid carcinoma after 30 and 40 years of achalasia, an incidence of 2.6%. This incidence is similar to that reported by others[9] but far less than Adams et al.[1] determined from a much longer followup period.

Although the numbers of patients who were not treated or who were initially treated with anticholinergic medication are small, the results support the general impression that achalasia neither spontaneously remits nor responds to medication.

Our results with dilatation by mercury-filled bougies are not encouraging. In contrast to the report by Benedict,[2] our patients did not obtain more than transient relief. Because of the 6% incidence of esophageal perforation, the belief that bougienage should be used in elderly or very ill patients deserves reappraisal. Also, the more complete and lasting relief obtained by pneumatic dilatation or esophagocardiomyotomy removes bougienage from consideration as a primary treatment for anyone able to undergo those treatments. The usefulness of such dilatation to facilitate endoscopic evaluation and subsequent pneumatic dilatation is not denied.

Because no single group of physicians treats all patients with achalasia who are at the University of Iowa Hospitals, our results indicate a lesser degree of success with pneumatic bag dilatation and esophagocardiomyotomy than others have reported.[6,10] But this situation allows a comparison of results of treatment for achalasia from a single institution. To the authors' knowledge, this type of comparison of treatment modalities has not been reported previously. Also, although it has been written that mercury bougienage is not beneficial in achalasia, there are no data to support this general impression and in fact as late as 1964, this form of treatment was suggested as a primary treatment modality.[2]

The only treatments of clear benefit to our patients were pneumatic dilatation and esophagocardiomyotomy.

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Erosive Hemorrhagic Gastroduodenitis with Fibrinolysis and Low Factor XIII

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Four patients with erosive hemorrhagic gastroduodenitis were found to have high fibrinolytic activity of the gastric juice. No increase in the fibrinolytic activity could be demonstrated in the circulating blood, but the values found for fibrinogen, plasminogen and α_2-macroglobulin were low. A high content of FDP was found in the serum. All patients had a markedly decreased content of factor XIII. Platelet count and other coagulation components were normal. These findings were interpreted as signs of *local* fibrinolysis in the diseased parts of the gastrointestinal canal. The bleeding stopped after oral and intravenous administration of a fibrinolytic inhibitor (AMCA Cyclokapron®) and of factor XIII-containing concentrate. In bleeding from gastroduodenal ulcer and esophageal varices, no increase in gastric fibrinolytic activity was found. It is suggested that the high local fibrinolytic activity in the stomach in erosive gastritis together with the low content of factor XIII contributes substantially to the hemorrhage in this condition. These observations may lead to a revision of the treatment of such cases.

EROSIVE HEMORRHAGIC GASTRODUODENITIS is a fairly rare cause of gastrointestinal bleeding occurring mainly in elderly people.

Various etiological factors have been reported, such as severe stress, trauma or surgery and drugs, such as acetylsalicylic acid, cortisone and antiphlogistics. In many cases no such factors are, however, demonstrable. Because of the often massive hemorrhages and the widespread mucosal lesions, treatment may be difficult.

This paper reports the occurrence of a high local fibrinolytic activity in the gastric juice in association with low factor XIII concentration in the blood in four patients with acute erosive hemorrhagic gastroduodenitis.

Case Reports

Case 1. A 90-year-old man, who had always been in extremely good health, was admitted to hospital on 18th August because of passage of large amounts of black stools. On admission he was pale but alert and had no pain. The rectal content was black. Rectoscopy did not reveal any source of bleeding. Four hundred ml of fresh and old blood was aspirated from the stomach via a gastroduodenal catheter. The bleeding episodes recurred the following two days. Laparotomy on the 21st of August revealed large amounts of blood in the oral part of the small intestine. A gastric resection according to Billroth II was performed. The gastric mucosa had normal appearance, but the duodenum was the site of severe acute ulcerative lesions, obviously the source of bleeding. Histological examination revealed erosive duodenitis.

The first two days after operation were uneventful, but an attack of respiratory distress and signs of sepsis developed on the third postoperative day and a new episode of massive hemorrhagic on the sixth. Vasopressin was infused without significant effect on the hemorrhage. The patient developed tubular necrosis with anuria followed by polyuria. Gastroscopy showed multiple superficial ulcerations in the remaining stomach. Based on results of coagulation and fibrinolysis studies treatment with fibrinolytic inhibitors (AMCA) and later with factor XIII concentrate was initiated, which controlled the bleeding. One week later massive gastric hemorrhage recurred. Bleeding was again almost completely controlled by the same treatment as before. Three and a half weeks after the operation the patient succumbed from bronchopneumonia and cardiac incompensation. The patient received 64 units of most of which was fresh blood.

Necropsy showed multiple gastric erosive lesions of the same type as seen in the operative specimen of the duodenum. No signs of thrombosis or embolism.

Case 2. A 70-year-old woman was admitted to hospital because of acute pancreatitis. She was treated with surgical exploration and drainage. Five days later the patient began to bleed heavily from the stomach. Her coagulation status was examined as well as the fibrinoly-

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TABLE 1. *Results of Coagulation Studies in Cases 2, 3 and 4.*

	Case 2	Case 3	Case 4	Normal values
Platelet number	130,000	250,000	310,000	150,000-400,000
Factor VIII (%)				
biol. activity		198	220	60-160
immunol.		248	480	60-175
P & P (%)	35	104	94	80-120
Factor V (%)	95	96	106	80-120
Fibrinogen (g/100 ml)	0.42	0.31	0.45	0.20-0.40
Antithrombin III (%)	50	72	84	60-140
Plasminogen (%)	35	60	35	60-140
α_2M (%)		74	49	80-120
FDP (μg/ml)	32	15	38	0-10
Ethanol gelation test	neg	neg	neg	neg
Factor XIII (units)	6	9	9	11-31
Gastric juice				
Fibrinolytic activity (lysed area in mm^2)				
unheated plates	1254	—	1200	0
heated plates	1080	—	730	0
FDP (μg/ml)	45	115	6000	0

tic activity of the gastric juice (Table 1). The bleeding was controlled by oral treatment with AMCA. This treatment was continued until the patient died from pancreatitis three days later without recurrence of the bleeding. Necropsy revealed erosive gastritis.

Case 3. A 77-year-old woman had a previous history of cardiosclerosis and arthrosis, for which she had been treated with indomethacin and cortisone. She was admitted with an acute severe gastrointestinal hemorrhage with hematemesis, severe tachycardia and low blood pressure. Gastroscopy 12 hours after admission showed multiple, bleeding erosive lesions in the stomach. Biopsy confirmed the suspicion of acute erosive and hemorrhagic gastritis. Coagulation studies were performed (Table 1). Based on these the patient was given AMCA orally and factor XIII-concentrate, which immediately controlled the bleeding. No further bleeding occurred, and the patient could be discharged after 10 days.

Case 4. A 60-year-old woman, previous to admission, had been healthy with the exception of a duodenal ulcer 24 years ago. She was admitted with a one day history of gastrointestinal hemorrhage with hematemesis and melena. During the first three days in hospital she was well, but then massive hemorrhage recurred. Laparatomy was performed. A small duodenal ulcer was found, as well as multiple hemorrhagic erosive lesions in the gastric mucosa. Pyloroplasty and vagotomy was done. The following day the patient started to bleed again. Gastric resection according to Billroth II was done. In the gastric mucosa multiple superficial ulcerations were found and the diagnosis erosive hemorrhagic gastritis could be confirmed histologically. Ten days later massive bleeding occurred. She was at that time considered inoperable. Coagulation studies were carried out (Table 1). Following oral treatment with AMCA the bleeding promptly stopped. The patient recovered slowly and was discharged one month later.

Methods

Platelet and coagulation studies. Platelet count, Ivy bleeding time, coagulation time, activated partial thromboplastin time (APTT), one-stage prothrombin time, factor V, prothrombin + factor VII + factor X (Owren's P & P-test), factor VIII (AHF) (biologic activity) and fibrinogen were determined with methods described earlier.[27,28] *Factor VIII* was also determined immunologically according to Holmberg and Nilsson.[19] *Antithrombin III* was determined immunochemically by the rocket method of Laurell.[15] The *thrombin time* and *Reptilase time* were performed as described by Latallo et al.[21] The *ethanol gelatin test* was used for determining fibrin monomers according to Godal et al.[12] *Factor XIII* (FSF) was measured by a slight modification[18] of the dansylcadaverine method of Lorand et al.[23] Normal range 11-31 FSF units/ml.

Fibrinolytic studies. The *fibrinolytic activity* of plasma and resuspended euglobulin precipitate was measured on unheated bovine fibrin plates, as described by Nilsson and Olow.[28,29] The pH of the *gastric juice* was first adjusted to 7.0 and the activity measured on both unheated and heated fibrin plates. *Plasminogen* was measured by an immunochemical method.[9] *Fibrin/fibrinogen degradation products* (FDP) were determined with the immunochemical method of Niléhn[14,25] in gastric juice and in serum samples obtained from blood collected with EACA and thrombin. In some samples the FDP were typed in the way described by Bouma et al.[4] α_2– macroglobulin (α_2M) was determined as previously described.[16] The concentration of *AMCA* in serum was determined by a clot lysis method described by Nilsson, Sjoerdsma and Waldenström.[30] For determination of AMCA in urine a method described by Andersson et al.[1] was used. It is based on high voltage paper electrophoresis and photometric determinations of the ninhydrin complex.

Material

Fraction I-O. This fraction is prepared by AB Kabi, Stockholm (AHF Kabi) according to the glycerine method of Blombäck and Blombäck.[3] It contains not only factor VIII and fibrinogen, but also factor XIII. The factor XIII content of one bottle (100 ml) corresponds approximately to that of 250 ml of plasma. *AMCA.*

Aminomethyl-cyclo-hexane-carbonic acid (Cyclokapron®, AB Kabi) for intravenous and oral administration. *Plasmin.* Human plasmin (Kabi DTC 48; Grade A, AB Kabi, Stockholm). *EACA.* EACA solution from AB Kabi, containing 0.1 g EACA/ml. *Trypsin.* (Trypure, AB Novo), Dissolved in 0.9% NaCl. *Aprotinin (Trasylol®, Bayer).* Solution containing 10,000 KIE/ml. Further dilutions with 0.9% NaCl. *Pepsin.* (B.D.H. Laboratory Chemical Division). Dissolved in 0.9% NaCl.

Results of Coagulation Analyses

Case 1. The results of the coagulation analyses and some other relevant data in Case 1 are given in Fig. 1.

At the first examination (Aug. 19th, 1974) the platelet count and the values found for P & P, factor V, antithrombin III, thrombin time, plasminogen and α_2M were normal. The fibrinogen level was 0.25 g/100 ml. The factor VIII level was normal when determined with a biological method, but raised when assessed with an immunological procedure. The FDP level in serum was low (7.5 μg/ml). No fibrinolytic activity could be demonstrated in the circulation. The factor XIII content (13 FSF units) was in the lower part of the normal range. The ethanol gelation test was negative.

Two days after gastrectomy the coagulation system was found to be impaired. Analyses performed on August 22nd and 23rd thus showed a low platelet count. The fibrinogen level had not risen after the operation. The values found for antithrombin III, α_2M and plasminogen had decreased, and the amount of FDP (25 μg/ml) in the serum had increased. The thrombin time and the Reptilase time were normal. The ethanol gelatin test was possibly positive. These findings suggested that the patient had proteolysis with activation of the coagulation as well as of the fibrinolytic system.

The patient was given heparin and AMCA on August 23rd to 26th, during which the platelet count increased continuously. Also the values found for fibrinogen, plasminogen and α_2M increased.

Examination of the coagulation system on August 26th to 28th in association with massive gastric hemorrhage indicated an activation of the fibrinolytic system. The platelet count was normal or slightly decreased. P & P was somewhat low, but promptly rose after administration of Vitamin K. The factor V level was normal. The AHF levels, especially when determined with the immunochemical method, were high. The fibrinogen fell substantially to 0.19 g/100 ml and the plasminogen to 20%. Antithrombin III did not fall further. α_2M was as low as 25%. The patient had FDP in the serum. The FDP were of low molecular weight type, i.e. D– and E–products. Factor XIII was low, 9 FSF units. Examination of the blood on fibrin plates showed no fibrinolytic activity. The ethanol gelatin test was negative.

The gastric juice showed high fibrinolytic activity on both unheated and heated fibrin plates (Table 2). The activity was slightly lower on heated plates. Addition of EACA (10 mg/ml) to the gastric juice reduced the activity by about 80%. The plasmin level of the gastric juice was determined with Laurell's rocket method.[14] The activity of the gastric juice corresponded to that of about 5 CTA units of plasmin. The juice also contained a substantial amount of FDP (D + E products). The fibrinolytic activity was neutralized by administration of AMCA locally in the stomach.

Intense intravenous and later oral therapy with AMCA was started on August 29 with simultaneous control of the concentration of AMCA in the serum and urine. Maintenance of the serum AMCA at a level between 4-10 μg/ml required AMCA in a dose of 6-10 g a day. The patient had polyuria and excreted 50-90% of the AMCA in the urine.

Factor XIII was repeatedly found to be low (Fig. 1). On August 31st and September 1st the patient was given factor XIII (fraction I-O) in a dose corresponding to that in 2,000 ml of normal plasma.

During treatment with AMCA and factor XIII concentrate the fibrinogen content rose to levels above 0.50 g/100 ml. α_2M increased and FDP in the serum fell substantially. P & P and factor V persisted unchanged, and antithrombin III did not decrease. Factor XIII rose to normal level.

For irrelevant reasons the patient was given AMCA only sporadically between September 6th-8th. On September 8th he again showed signs of fibrinolysis and bled copiously. The fibrinogen content fell to 0.36 g/100 ml. The FDP in the serum rose to 35 μg/ml and the α_2M fell. The fibrinolytic activity of the gastric juice was high. The platelet count, P & P and factor V remained normal. The ethanol gelation test was negative. The factor XIII content decreased to 5 FSF units/ml.

TABLE 2. *Studies on Gastric Juice From Case 1.*

Date	Gastric juice	Unheated plates mm^2	Heated plates mm^2	FDP μg/ml	Plasmin CTA units/ml
31/8		812	500	1000 (D + E)	5
31/8	Addition of 10 mg EACA per ml gastric juice	210			
1/9	After administration of AMCA locally in the stomach	75	0	0	0
1/9	8 hours after AMCA locally	960	400	0	5
3/9		820	360	800 (D + E)	2
9/9		361		3560 (D + E)	
11/9		890		810	
14/9		1311			

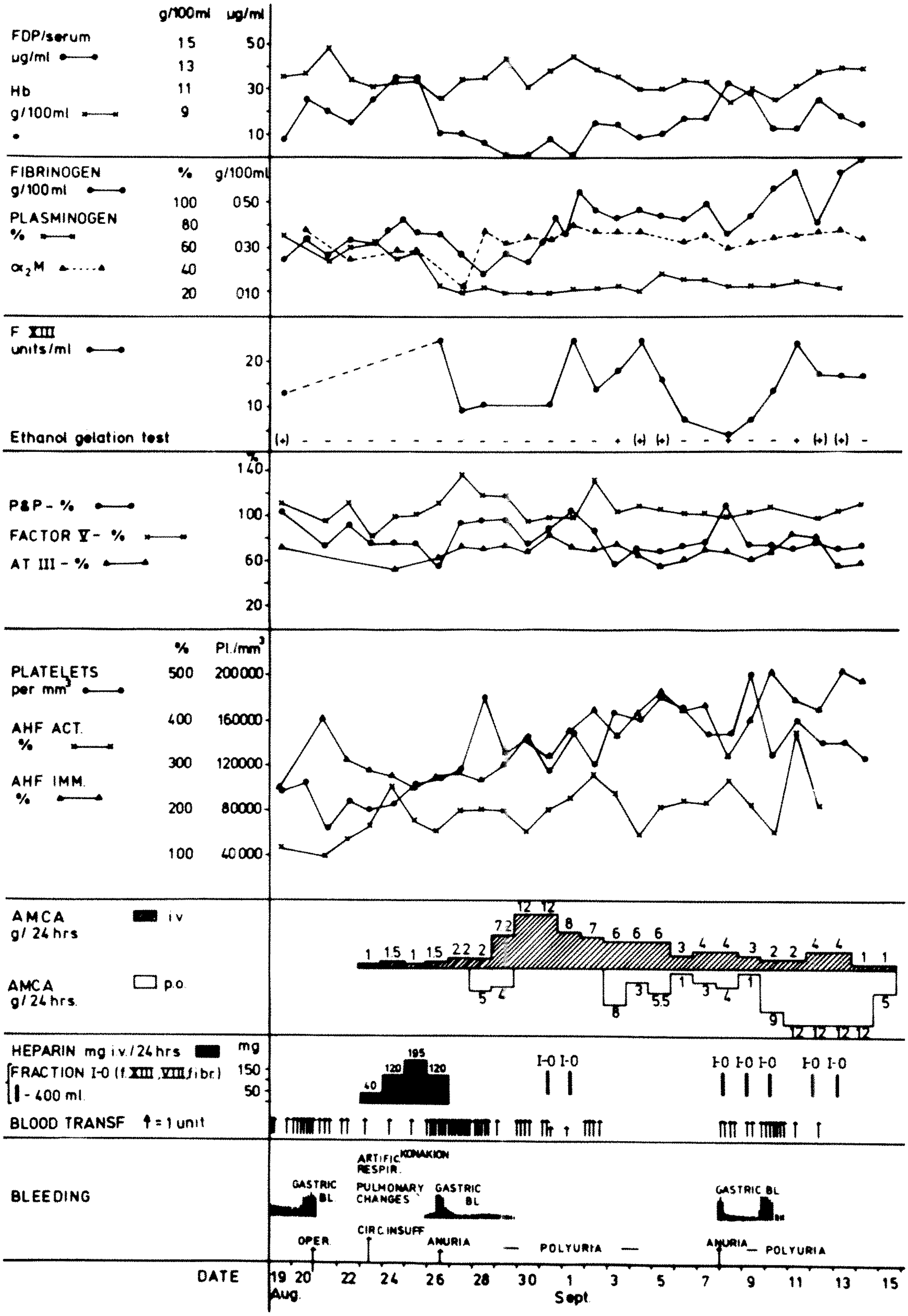

FIG. 1. Pertinent data on laboratory findings, therapy and course in Case 1.

From September 10th the patient received AMCA by mouth at short intervals (Fig. 1) and factor XIII concentrate daily. The fibrinogen values rose to high levels. The factor XIII content became normal. On one occasion the ethanol gelation test was positive. The platelet count remained normal as did P & P and factor V. Throughout the disease the patient had a high level of AHF related protein. The thrombin and Reptilase times were normal throughout, except for prolongation of the thrombin time during treatment with heparin. The fibrinolytic activity of the blood was not increased.

Cases 2, 3 and 4. The results of the coagulation analyses on the 3 other cases with erosive gastritis are given in Table 1. In these patients the platelet count, P & P and factor V were normal. The factor VIII related antigen was high. The plasminogen, α_2M and factor XIII were decreased, and the FDP in the circulation was increased. The gastric juice showed increased fibrinolytic activity particularly on unheated fibrin plates.

Examination of Gastric Juice From Non-bleeding Patients.

Gastric juice obtained from 15 patients (referred for the pentagastrin test) without gastric hemorrhage were examined. The samples exhibited little or no fibrinolytic activity on fibrin plates.

Gastric juice from patients with upper intestinal tract bleeding due to other causes was examined. Four patients with massive hemorrhage from a verified gastric or duodenal ulcer were studied with regard to their fibrinolytic activity in the gastric juice. Three of them had no activity at all, and one had a very slight activity compared with the patients with erosive gastritis. Factor XIII was not decreased in any of these patients.

To differentiate the plasmin activity in the gastric juice in the patients with erosive gastritis from that of other gastric enzymes with proteolytic activity the effect of plasmin (9.4 and 4.7 CTA units/ml), trypsin (100 and 10 µg/ml) and pepsin (10-400 µg/ml) on unheated and heated fibrin plates was determined with and without EACA (0.1 and 10 mg/ml) and with and without Trasylol® (1, 10 and 100 KIE/ml). Pepsin showed no fibrinolytic activity on fibrin plates at pH 7. Plasmin exhibited three times as much activity on unheated plates, as on heated plates. Trypsin showed activity, which was roughly equal on heated and unheated plates. EACA in the doses used suppressed the effect of plasmin by about 50%, but had no demonstrable effect on the activity of trypsin. Trasylol inhibited both trypsin and plasmin, the inhibition varying with the dose given.

Discussion

Most human tissues contain fibrinolytic activators,[2] mainly in the small vessels.[31] The fibrinolytic activity of the gastric mucosa has received relatively little attention. A plasmin-like activity was however, found by Cox et al. in the gastric veins in patients with gastric haemorrhage. The plasmin-like enzyme in blood from the gastric vein in such patients has recently been identified as plasmin.[32]

Disseminated intravascular coagulation has been claimed to be of pathogenetic significance for developing erosive gastritis.[24,13] This could not be confirmed in the present study. The first case showed signs of activation of the coagulation process but only in the early postoperative course. This patient developed a peripheral circulatory collapse in combination with thrombocytopenia and positive ethanol gelation test indicating the presence of fibrin monomers in the circulation which is claimed to be typical for DIC.[26] Heparin also produced some improvement in the patient's coagulation status. During the further course the laboratory findings suggested an activation of the fibrinolytic system rather than of the coagulation system. The patient thus had a normal platelet count, negative ethanol gelation test, normal P & P and factor V and high factor VIII, but the values for fibrinogen, plasminogen and α_2M were low. It is well known that α_2M can bind both plasmin and thrombin[11] and thus fall when the coagulation system or the fibrinolytic system is activated. Antithrombin III was normal. The patient had a high content of FDP in serum which decreased during adequate AMCA-treatment. No increase in the fibrinolytic activity could be demonstrated in the circulating blood. The fibrinolytic activity of the gastric juice was, however, high. This activity was due to a plasmin-like enzyme and not to other gastric proteolytic enzymes. We interpret these findings in the blood and gastric juice as compatible with the presence of local fibrinolysis in the stomach and duodenum but without a generalized fibrinolysis. On passage of the blood through the stomach and duodenal wall activators are released to the blood and the plasminogen is transformed, at least locally, to plasmin, which breaks down fibrinogen and fibrin. The activators and the plasmin are neutralized by inhibitors, such as α_2M, in the general circulation and therefore no activity can be measured in the circulation. This is in good agreement with the findings[6,32] of plasmin-like enzyme in the gastric vein but not in the gastric artery or peripheral veins. In such cases plasminogen activators and/or plasmin must also enter the gastric juice, causing dissolution of the hemostatic thrombi which successively form in the eroded areas of the duodenum and stomach. In this way the local activation of the fibrinolytic system contributes to a continuation of the hemorrhage. The effect of administration of AMCA

It is of interest to note that the factor XIII content was low in all four patients. Hedner et al.[17] measured factor XIII with the specific dansylcadaverine method of Lorand et al.[23] in patients with various diseases. They found low levels in patients with sepsis and other conditions associated with abnormal proteolytic activity (fibrinolysis and/or activation of the coagulation system). No correlation was found between the factor XIII and the fibrinogen values or the levels of FDP which suggested some specific degradation of factor XIII unrelated to the fibrinogen degradation. Egbring et al.[8] produced evidence that factor XIII can be degraded by proteases in the leukocytes. It is not known why the factor XIII level is low in erosive gastritis, but the mechanism responsible is probably the same as that in other cases of abnormal proteolysis. The rapid decline in factor XIII seen in case 1 in connection with the bleeding episodes is noteworthy and supports this assumption.

Factor XIII is necessary to stabilize the fibrin structure. A non-stabilized fibrin clot is more readily dissolved by urokinase activated plasminogen than a stabilized one.[10,22] The low factor XIII levels in our patients with erosive gastritis must thus render the clots formed in the stomach more susceptible to the local fibrinolytic activity with aggravation of the bleeding as a result. In our first patient and in one of the others (case 3) infusion of factor XIII containing fraction I-O together with administration of AMCA, also seemed to be of benefit. The AHF level and especially AHF protein were markedly increased in these patients. A high AHF level is a sensitive sign of abnormal tissue destruction.[20] No side effects to the treatment with AMCA were observed. No patient developed thrombus.

In those patients with erosive gastritis and duodenitis, then, the local fibrinolytic activity in the stomach was high and the factor XIII content low, while similar abnormalities were not found in patients with gastroduodenal haemorrhage due to an ulcer. There is reason to assume that these disturbances contributed substantially to the markedly increased bleeding tendency. These observations may lead to a revision of the treatment of such cases. If it is known from the very beginning that the patient has an erosive gastroduodenitis with high fibrinolytic activity in the stomach he should receive adequate antifibrinolytic treatment both i.v. and by mouth and also be treated with factor XIII. Such measures might make operation unnecessary, which is of particular importance in these elderly patients with diffuse erosive lesions in the stomach and duodenum.

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Phosphate Depletion and Repletion:

Relation to Parenteral Nutrition and Oxygen Transport

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Phosphate depletion occurring during total parenteral nutrition has been frequently reported during the past 4 years. Hypophosphatemia may be associated with confusion, hyperventilation, and neuromuscular irritability, suggesting a total body phosphate deficiency. If inorganic phosphate levels fall below 1.0 mg %, diminished red cell glycolysis occurs with low erythrocyte levels of 2, 3 diphosphoglycerate and adenosine triphosphate. Lowered red cell organic phosphates are associated with increased hemoglobin oxygen affinity. If severe hypophosphatemia occurs, hemolytic anemia, which is correctible by phosphate infusion, may result. In addition, leucocyte function is impaired by low levels of serum inorganic phosphate. While recognized as a needed additive, recommended phosphate supplements vary. Different infusion regimens have been suggested over the past 4 years, based primarily on assumed daily requirements. In the 19 trauma patients described who received hyperalimentation as part of their treatment, phosphate administration was calculated retrospectively and prospectively as a function of non-protein calories infused. Four different groups were studied. Group A received no phosphate additive and quickly became severely hypophosphatemic. Group B received from one to 15 meg of potassium acid phosphate per 1,000 K cal and developed a more gradual lowering of serum inorganic phosphate levels. Group C received 15 to 25 meg of potassium acid phosphate per 1,000 K cal and maintained normal phosphate levels throughout the course of treatment. Group D received greater than 25 meq of potassium acid phosphate per 1,000 K cal and gradually increased their serum inorganic phosphate levels. A significant positive correlation was found between serum inorganic phosphate levels, 2, 3 diphosphoglycerate levels, adenosine triphosphate levels, and P_{50} of the oxy-hemoglobin dissociation curve. No patients developed hemolytic or neuromuscular syndromes which were attributable to hypophosphatemia. This study describes a simple method for the maintenance of adequate phosphate levels in patients whose dextrose-protein solutions may vary from day to day, by relating it to non-protein calories. Provision of 20 to 25 meq of potassium dihydrogen phosphate per 1,000 K cal will maintain normal serum levels of inorganic phosphate during total parenteral nutrition.

THE BODY POOL of phosphorus is in dynamic equilibrium with phosphate containing energy substrates. Patients in negative nitrogen balance, from starvation or injury, have excessive urinary loss of phosphate but maintain normal serum inorganic phosphate levels.[10] Serum inorganic phosphate levels directly affect the rate of red cell glycolysis and formation of adenosine triphosphate (ATP) and 2, 3 diphosphoglycerate (2, 3 DPG).[26] Erythrocyte organic phosphates, primarily 2, 3 DPG and ATP, interact with hemoglobin to diminish its oxygen affinity.[2,5,7] The relation between oxygen saturation and red cell organic phosphate values is linear and inverse. High affinity of oxygen for hemoglobin, secondary to many clinical conditions, may result in tissue hypoxia.[22]

Many conditions have been described in which red cell glycolysis is altered by high or low serum inorganic phosphate levels. Hyperphosphatemia, as occurs in uremia, during recovery from transfusion and following phosphate infusion, results in a rise in 2, 3 DPG and ATP with a consequent shift to the right of the oxy-hemoglobin dissociation curve.[16,33,34] Oxygen transport compensation for sickle cell and childhood anemia may occur through elevated serum inorganic phosphate levels.[6,21]

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TABLE 1. *Phosphate Infusion Regimens Recommended*

Author, Year	Dosage of Potassium Acid Phosphate
Parsa, et al. (1971)[23]	20 meq/1,000 K cal
Meng and Sandstead (1971)[20]	As indicated
Sedgwick and Viglotti (1971)[31]	$\frac{\text{4-10 meq}}{\text{1,000 K cal}}$
Dudrick, et al. (1972)[9]	$\frac{\text{10-15 meq}}{\text{1,000 K cal}}$
Shils (1972)[35]	300-400 mg/day (orthophosphate)
Kaminski (1972)[14]	20 meq/1,000 K cal
Sheldon (1973)[32]	20-25 meq KH_2PO_4/1,000 K cal
Jacob (1974)[8]	3 meq/kg
Blackburn (1974)[3]	30-60 meq/KH_2PO_4/day

Hypophosphatemia is associated with diminished red cell ATP and 2, 3 DGP values.[17,25] Recently, Jacob demonstrated acute hemolytic anemia associated with serum inorganic phosphate levels less than 1.0 mg per 100 ml.[13] Parenteral phosphate administration corrected the hemolytic process and restored low DPG and ATP levels to normal. Jacob has subsequently reported white cell dysfunction associated with hypophosphatemia.[8] Hypophosphatemia may occur secondary to alcoholism, ingestion of phosphate binding antacids, hyperparathyroidism, and diabetic keto-acidosis.[1,4,38]

Lichtman and other authors have reported hypophosphatemia, increased hemoglobin oxygen affinity and diminished levels of red cell organic phosphates secondary to total parenteral nutrition.[18,24,36,39]

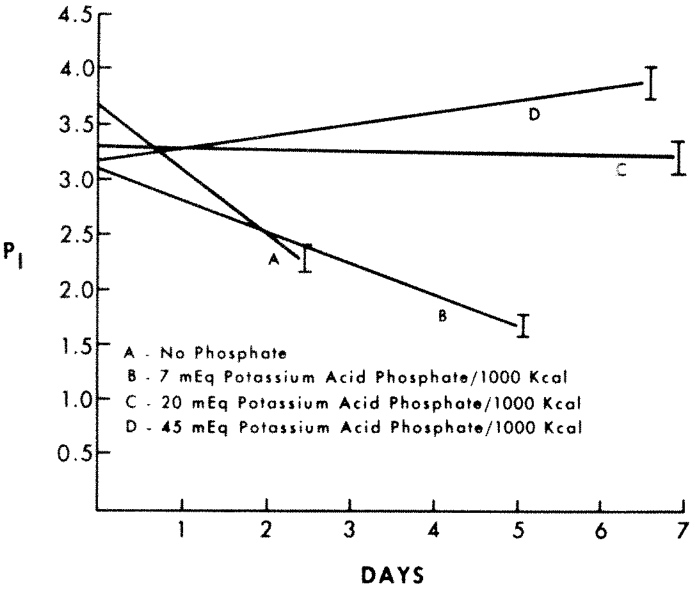

FIG. 1. The results of serum P_i levels in the four phosphate infusion regimens are illustrated. Without phosphate additives (Group A), significant hypophosphatemia develops. Group B (< 15 meq KH_2PO_4/1,000 K cal) phosphate levels fall but remain above 1.0 mg%. Group C (15 to 25 meq KH_2PO_4/1,000 K cal) resulted in maintenance of normal P_i levels. Group D (>25 meq KH_2PO_4/1,000 K cal.) resulted in elevation of serum inorganic phosphate levels.

Intravenous provision of dextrose and protein split products or amino acids, if phosphate is not added, will result in significant hypophosphatemia within 3 days and profound hypophosphatemia in 10 days.

Although recognized as a needed additive, different infusion regimens have been recommended over the past 4 years (Table 1). It is difficult to compare the schedules because the forms of phosphate available for intravenous infusion are multiple and phosphate exists biologically in both mono valent (H_2PO_4-) and divalent ($HPO_4=$) forms. Consequently, the potential for producing hypophosphatemia, in spite of phosphate addition, exists. These studies were performed to establish clinically useful phosphate requirements in patients receiving total parenteral nutrition. During phosphate depletion, repletion, and maintenance, administered phosphate was related to calculated caloric intake.

Material and Methods

Nineteen patients receiving hypertonic dextrose and fibrin hydrolysate parenteral nutrition solution were studied. No intrinsic phosphorus compounds are included in this particular preparation.*

All patients were trauma victims and were receiving hyperalimentation under the direction of their physicians as a specific component of their care. All patients had baseline phosphorus levels which were normal prior to the institution of parenteral nutrition. No patient intentionally received phosphate-free total parenteral nutrition. Eight patients, however, received dextrose-fibrin hydrolysate without phosphorus compounds and became hypophosphatemic. The calories received were retrospectively calculated and phosphate repletion successfully accomplished. No patient in renal failure was studied. Potassium, vitamins and calcium were administered as clinically indicated.

Patients were divided into four groups. In Group A, patients initially received no calcium or phosphate in their hyperalimentaiion solutions. Group B received less than 15 meq of potassium acid phosphate† per 1,000 K cal. Group C received 15 to 25 meq of potassium acid phosphate per 1,000 K cal, and Group D received greater than 25 meq of potassium acid phosphate per 1,000 K cal.

When hypophosphatemia occurred in any of these groups, potassium acid phosphate (meq) in additional or corrective amounts was added to their hyperalimentation solutions. The number of non-protein calories each patient received was calculated using the following formula: one gram of carbohydrate = 3.5 K cal.

Daily determinations of calcium and phosphorus (Ca and Pi) were performed, as were erythrocyte glycolytic intermediates (2, 3 DPG and ATP). In addition, partial pressure of oxygen at which hemoglobin is 50% saturated (normal $P_{50} = 26.1 \pm 1mm_{Hg}O_2$) was performed daily.

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* Aminosol (Abbott)

† McGaw Catalogue #W1140.

Calcium and phosphorus (normal $P_i = 2.8 - 4.0$ mg%) determinations were performed on the auto analyzer. Diphosphoglycerate (normal DPG = 11.9 ± 1.3 $\mu m/gm_{Hg}$) was measured using Keitt's Enzymatic method.[12] ATP (normal ATP = 2.9 ± 0.4 $\mu m/gm_{Hb}$) was assayed using a commercial enzymatic method (Cal Biochem). The oxyhemoglobin dissociation curve was measured spectrophotometrically following the equilibration of whole blood with balanced gas mixtures containing oxygen, CO_2 and nitrogen. The half saturation point of hemoglobin was then calculated using the Hill equation.[10]

Results

Infusion Regimens (Table 2, Fig. 1)

Group A: Infusion with a solution containing no phosphate; the 8 patients who received no phosphate initially in their infusion were all initially normophosphatemic with a mean serum $P_i = 3.7 \pm 0.6$ mg%. Within one to 5 days after 3,175 ± 2,700 K cal were administered, the mean serum P_i fell to 2.3 ± 0.7 mg%.

A significant correlation between total calories administered and the fall in serum P_i from pre-hyperalimentation levels was obtained on 15 samples in eight patients ($r = 0.67$; $P < .01$) (Fig. 2).

A significant correlation between the serum P_i and the number of calories administered in the previous 24 hours was obtained on 23 samples in 8 patients ($r = -0.67$; $P < 0.001$) (Fig. 3).

Group B: Infusion with a solution containing greater than zero but less than 15 meq potassium acid phosphate per 1,000 K cal; all 5 patients were initially normophosphatemic ($P_i = 3.1 \pm 0.5$ mg%). They received between two and 14 meq potassium acid phosphate per 1,000 K cal from one to 7 days and became hypophosphatemic ($P_i = 1.7 \pm 0.4$ mg%).

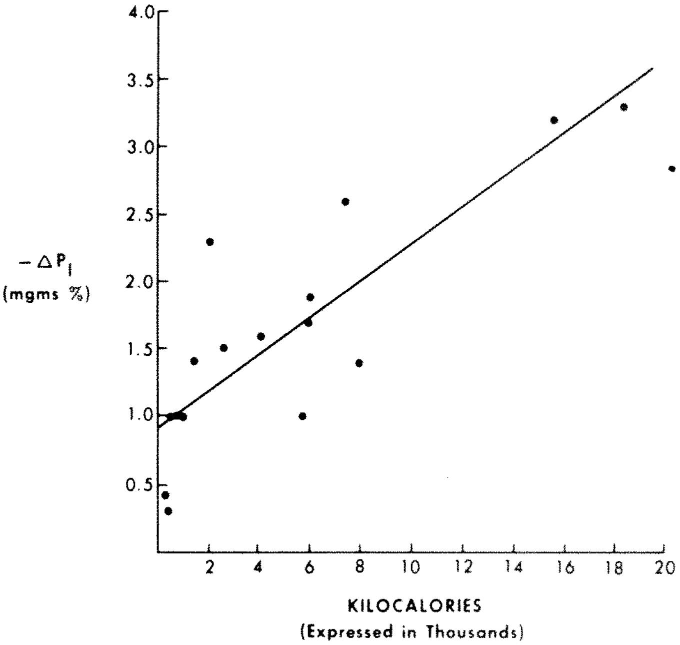

FIG. 2. A significant correlation was obtained between total calories administered and the *fall* in serum inorganic phosphorus from pre-hyperalimentation levels in patients who received infusions without phosphate supplementation ($r = 0.67$, $P < 0.01$).

Group C: Infusion with a solution containing between 15 to 25 meq potassium acid phosphate per 1,000 K cal; eleven of 12 patients were initially normophosphatemic ($P_i = 3.3 \pm 0.7$ mg%). They received between 15 and 25 meq potassium acid phosphate per 1,000 K cal from two to 22 days and remained normophosphatemic ($P_i = 3.2 \pm 0.8$ mg%).

Group D: Infusion with a solution containing greater than 25 but less than 152 meq potassium acid phosphate per 1,000 K cal; fourteen patients were initially slightly hypophosphatemic or normophosphatemic ($P_i = 3.2 \pm 0.8$ mg%). They received greater than 25 meq potassium acid phosphate per 1,000 K cal from two to 17 days and remained normophosphatemic or became hyperphosphatemic ($P_i = 3.9 \pm 1.0$ mg%).

TABLE 2. *Phosphate Infusion Regimen*

Patient Groups	Group A Zero Phosphate	Group B <15 meq Potassium Acid Phosphate/1000 K cal	Group C 15.25 meq Potassium Acid Phosphate/1000 K cal	Group D >25 meq Potassium Acid Phosphate/1000 K cal
P_i at start of study (mg%)	3.7 ± 0.6	3.1 ± 0.5	3.3 ± 0.7	3.2 ± 0.8
P_i at end of study (mg%)	2.3 ± 0.7	1.7 ± 0.4	3.2 ± 0.8	3.9 ± 1.0
Number of days of infusion	2.4 ± 1.3	4.4 ± 2.7	6.9 ± 5.5	6.5 ± 4.5
Exact phosphate dosage (meq/1000 K cal)	0	6.7 ± 5.4	19.8 ± 3.1	44.5 ± 19.5
Number of Patients	8	5	12	14

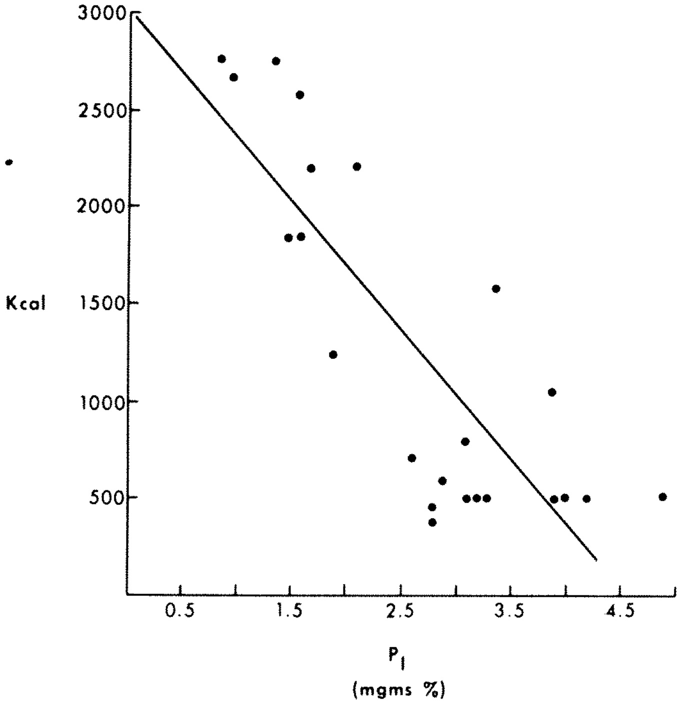

FIG. 3. A significant correlation was obtained between the serum inorganic phosphorus levels and the number of calories administered in the previous 24 hour period to patients receiving infusions without phosphate supplementation (r = −0.67; P<0.0001).

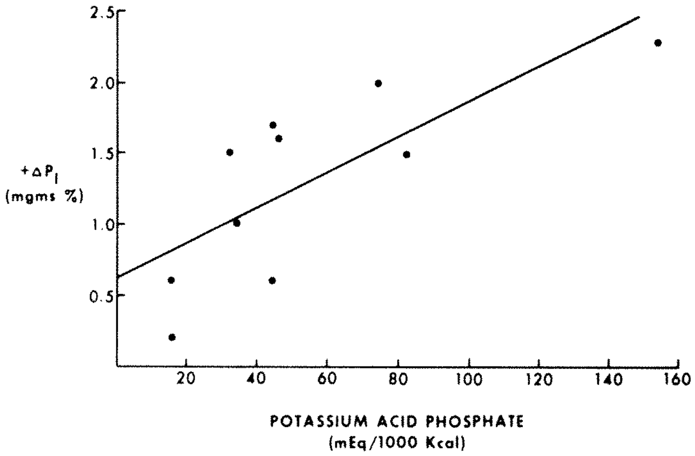

FIG. 4. A significant correlation was found between the phosphate concentration infused and the positive change in serum inorganic phosphorus above baseline hypophosphatemic levels on samples taken from patients during repletion from acute hypophosphatemia (r = 0.60; P<0.05).

Repletion of Hypophosphatemic Patients (Table 3 and Fig. 4)

The infusion of between 15 and 152 meq potassium acid phosphate per 1,000 K cal from one to 5 days resulted in an increase of P_i from 1.9 ± 0.5 mg% to 3.2 ± 1.0 mg% in 8 patients who had become acutely hypophosphatemic. The change in P_i was paralleled by changes in P_{50}, ATP, and 2, 3 DPG (Table 4).

A significant correlation between the potassium acid phosphate concentration infused and the change in P_i above baseline hypophosphatemic levels was obtained on 11 samples in 8 patients (r = 0.60; P<0.05).

Erythrocyte Metabolism and Oxygen Transport (Table 4)

Hypophosphatemia (P_i = 1.3 ± 0.3 mg%) was associated with low or borderline normal ATP (2.1 ± 0.8 μm/gm H_b) and 2, 3 DPG (10.5 ± 1.7 μm/gm H_b) levels. In normophosphatemic and hyperphosphatemic patients, the ATP and DPG levels were normal or high. The mean P_{50} in each of these three groups of patients remained normal or above (Table 4) except for severely hypophosphatemic patients.

A significant correlation between serum P_i and ATP was obtained on 25 samples taken from 10 patients during the peak of and recovery from hypophosphatemia (r = 0.84; P<0.001) (Fig. 5). A significant positive correlation between 2, 3 DPG and P_{50} values occurred (r = 0.536; P<0.001). A significant positive correlation was found between P_i and P_{50} values (r = 0.541; P<0.001). A significant correlation between serum P_i and 2, 3 DPG was obtained on the same 25 samples taken from 10 patients during the peak of and recovery from hypophosphatemia (r = 0.64; P<0.001) (Fig. 6).

Discussion

This study suggests that cellular incorporation of inorganic phosphate during total parenteral nutrition is calorically dependent. A simple formula for phosphate supplementation based on non-protein calories of solution infused is described which anticipates phosphate needs and prevents depletion.

Lowering of serum inorganic phosphate levels occurred in the two groups in which the amount of phosphate

TABLE 3. *Repletion of Hypophosphatemic Patients*

	P_i (mg%)	P_{50} (mm_{Hg})	ATP (μm/gm Hb)	DPG (μm/gm Hb)
Initial Value	1.9 ± 0.5	24.7 ± 3.6	2.82 ± 1.0	14.2 ± 4.6
Values Following Repletion	3.2 ± 1.0	25.8 ± 2.0	3.60 ± 0.8	16.2 ± 3.7
Number of Patients:	8			
Days of Infusion:	1.6 ± 1.2 (Range = 1-5 days)			
Phosphate Dosage:	51 ± 40 meq Potassium Acid Phosphate/1,000 K cal Range = 15-152 meq Potassium Acid Phosphate/1,000 K cal			

TABLE 4. *Comparison of All Patients According to Serum Inorganic Phosphorous Levels*

	Normal Values	Hypophosphatemic Patients	Normophosphatemic Patients	Hyperphosphatemic Patients
P_i (Mg%)	2.6 to 4.3	1.3 ± 0.3	3.4 ± 0.5	4.6 ± 0.1
P_{50} (mmHg)	26.2 ± 1	25.8 ± 2.4	24.9 ± 2.3	25.5 ± 1.5
DPG (μm/gm Hb)	11.9 ± 1.3	10.5 ± 1.7	16.9 ± 2.8	17.2 ± 3.6
ATP (μm/gm Hb)	2.9 ± 0.4	2.11 ± 0.78	3.43 ± 1.25	4.19 ± 0.78
Hb (gm%)	12 to 16	11.2 ± 1.3	10.6 ± 2.2	10.6 ± 1.5
Number of Samples		12	58	9

received was less than 15 meq of KH_2PO_4 per 1,000 K cal in a 24-hour period. No significant change in serum inorganic phosphate levels occurred until 1,000 K cal of hypertonic dextrose and fibrin hydrolysate were administered.

Subsequent caloric increases were accompanied by a cumulative diminution of serum inorganic phosphate levels, suggesting phosphate deficiency is a function of caloric intake rather than time. Serum inorganic phosphate levels fell rapidly if no inorganic phosphate was provided (Fig. 7). A drop of 1 mg% or more in 24 hours occurred although the phosphate value remained within the normal range. At 48 hours, however, a substantial lowering of serum inorganic phosphate levels, in the range of 1-1.5 mg% was present. If phosphate administration was provided but was less than 15 meq per 1,000 K cal, the lowering of serum inorganic phosphate was less precipitous, but still occurred. Discontinuing the calorie protein solution for 24 hours resulted in a return to normal of serum inorganic phosphate levels.[29]

Repletion of 8 hypophosphatemic patients over one to 5 days with infusion of 15-152 meq of potassium dihydrogen phosphate per 1,000 K cal resulted in an increase in serum inorganic phosphate levels from 1.9 ± 0.5 mg% to 3.2 ± 1.0 mg%. If phosphate in excess of 20-25 K cal per 1,000 K cal was administered, serum inorganic phosphate levels increased above normal. Significant positive correlation between the amount of potassium dihydrogen acid phosphate administered and the serum inorganic phosphate levels measured suggests that repletion, as depletion, is calorically related. Repletion, then, of hypophosphatemic patients is based on the assumption of a

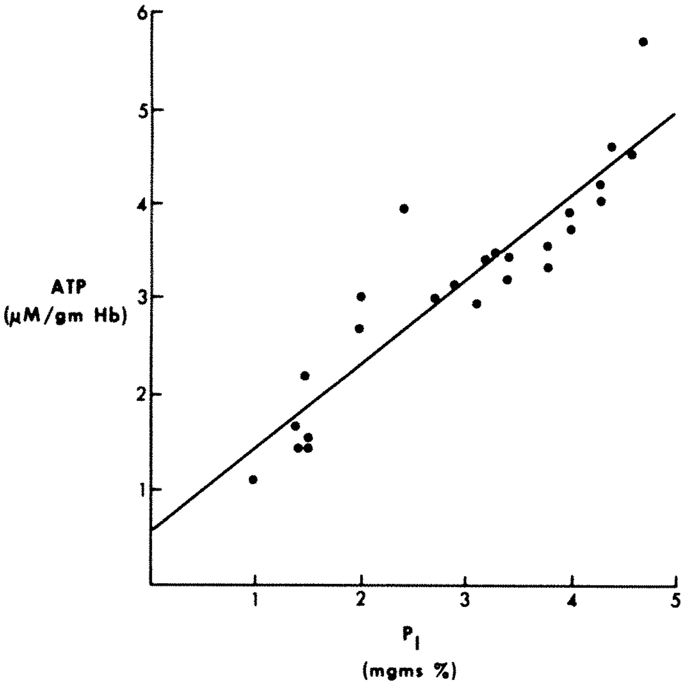

FIG. 5. A significant correlation was found between serum inorganic phosphorus and adenosine triphosphate on samples taken from patients during the peak of and recovery from hypophosphatemia (r = 0.84; P<0.001).

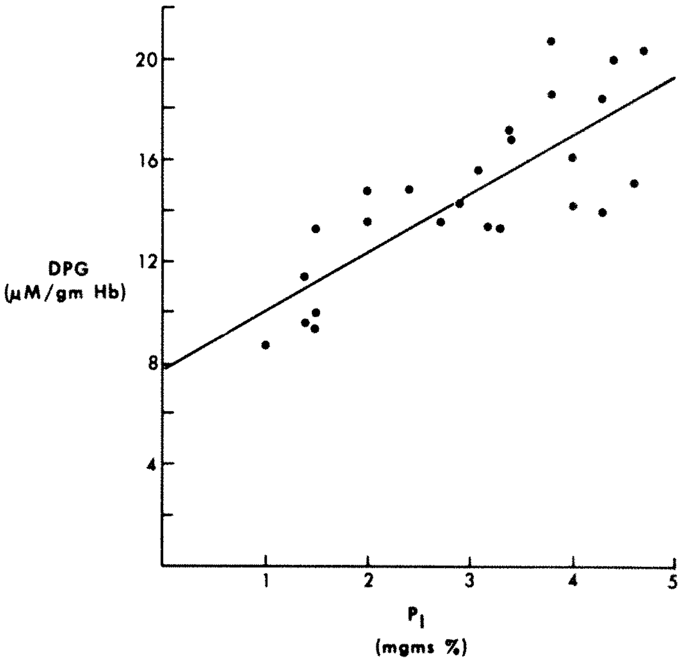

FIG. 6. A significant correlation was found between serum inorganic phosphorus and diphosphoglycerate on samples taken from patients during the peak of and recovery from hypophosphatemia (r = 0.64; P<0.001).

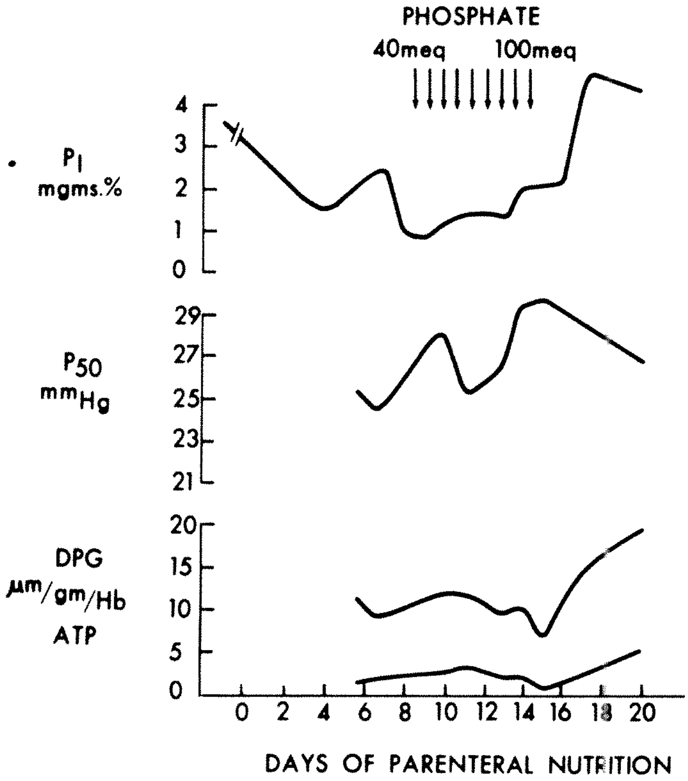

FIG. 7. Serum inorganic phosphate, erythrocyte glycolytic intermediates (DPG and ATP) and oxy-hemoglobin dissociation curves (P_{50}) in a patient with gastric fistula. Large quantities of phosphate were required to correct the calorie related deficit which occurred during 10 days of parenteral nutrition without phosphate.

cumulative phosphate deficit determined by the total kilocalories of solution administered.

The relation between red cell organic phosphates (ATP and DPG) and hemoglobin oxygen affinity is well known. The effect of extracellular inorganic phosphate levels on the regulation of red cell glycolysis was described prior to the understanding of the role of erythrocyte organic phosphate on oxygen transport. Rapoport and Guest first observed that rats on rachitogenic diets develop low levels of serum inorganic phosphate and decreased concentrations of red cell ATP and 2, 3 DPG.[25] They subsequently produced acidosis in humans by means of ammonium chloride diuresis and produced hyperphosphaturia, hypophosphatemia, and a decrease in red cell organic soluble phosphorus.[9]

Rose subsequently showed that the *in vitro* rate of erythrocyte glycolysis was directly related to extracellular inorganic phosphate concentration.[27] Our data suggest that *in vivo* regulation of red cell glycolysis is also related to serum inorganic phosphate levels (Fig. 8). A significant positive correlation occurred among serum inorganic phosphate, and red cell ATP, 2, 3 DPG and P_{50} values over a wide range of phosphate levels (P_i = 1.0 – 4.7 mg%).

It is unlikely that all phosphate depletion symptoms (weakness, malaise, obtundity, hyperventilation) are due to altered oxygen transport.[19] Specific abnormalities such as hemolytic anemia,[13] granulocyte dysfunction,[8] and erythrocyte glycolysis[23,32] are clearly associated with hypophosphatemia.

No patients in this study developed symptoms of phosphate depletion, hemolytic anemia, or identifiable increased susceptibility to infection. We attribute the absence of symptomatology to the avoidance of serum inorganic phosphate levels of less than 1.0 mg%, a level usually associated with complications such as hemolytic anemia. In addition, all patients in this study were anemic (mean Hemoglobin 10.7 gm) and would be expected to have elevation of erythrocyte glycolytic intermediates if adequate inorganic phosphate was present.[38]

Confusion regarding phosphate supplementation is based on the assumption of an identifiable daily requirement. Since profound hypophosphatemia must occur prior to the evolution of cellular defects, most recommended phosphate schedules will prevent extreme changes. It appears preferable, however, to maintain normal serum inorganic phosphate levels by providing 20-25 meq of phosphate for every 1,000 K cal of solution administered. Our practice is to use the potassium salt (KH_2PO_4) if the patient is not uremic or hyper-

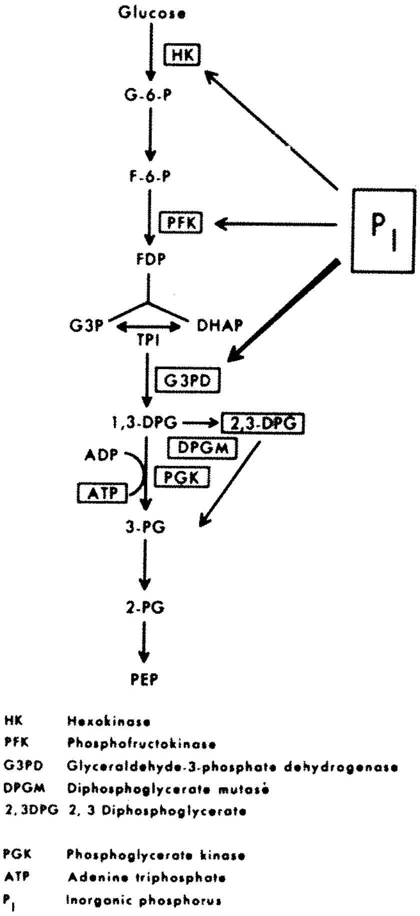
Glucose
HK
G-6-P
F-6-P
PFK
FDP
G3P
DHAP
TPI
G3PD
1,3-DPG
2,3-DPG
DPGM
ADP
PGK
ATP
3-PG
2-PG
PEP
P_I
HK Hexokinase
PFK Phosphofructokinase
G3PD Glyceraldehyde-3-phosphate dehydrogenase
DPGM Diphosphoglycerate mutase
2,3DPG 2, 3 Diphosphoglycerate
PGK Phosphoglycerate kinase
ATP Adenine triphosphate
P_I Inorganic phosphorus

FIG. 8. Emdem-Myerhoff pathway of glucose metabolism in the erythrocyte. An increase in extracellular inorganic phosphorus stimulates glucose uptake and lactate production in the erythrocyte by increasing the rate of the phosphofructokinase and hexokinase reactions. Another primary effect of inorganic phosphorus is at the glyceraldehyde 3-phosphate dehydrogenase step where P_i acts as a cofactor. Under normal conditions, the formation of 2, 3 DPG (via the diphosphoglycerate mutase step) is favored over that of ATP (the phosphoglycerate kinase step). Hyperphosphatemic states are associated with increased concentrations of ATP and DPG. Hypophosphatemic states are associated with decreased levels of ATP and DPG and increased levels of triose-phosphates.

kalemic, in which instance sodium salt is used. Prospective calculation of the non-protein calories to be provided will allow maintenance of normal serum inorganic phosphate levels.

Phosphate depletion secondary to total parenteral nutrition is a preventable iatrogenic complication. If appropriate phosphate supplementation is provided, the harmful effects of hypophosphatemia should become an interesting biochemical aberration of a useful clinical tool—total parenteral nutrition.

Since acceptance of this manuscript, Rudman, et al. have found that repletion of protoplasm is retarded or abolished if nitrogen, phosphate, potassium, or sodium are omitted from hyperalimentation solutions.[29]

Acknowledgment

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A Comparison In Vivo of Dacron Wool (Swank) and Polyester Mesh (Pall) Micropore Blood Transfusion Filters in the Prevention of Pulmonary Microembolism Associated with Massive Transfusion

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Experiments were performed to compare the effectiveness in vivo of the two most widely used micropore blood transfusion filters in preventing detrimental physiologic changes associated with transfusion of microaggregate-containing blood. Exchange transfusion with stored blood having an elevated screen filtration pressure (SFP) through polyester mesh (Pall) filters (Group PM) was followed by decreases in arterial blood pH and O_2 consumption, increases in arterial blood pyruvate and lactate concentrations, and a decrease in pulmonary DO_2. The lungs of 5 of 6 animals revealed emboli far out in the pulmonary microcirculation. These changes did not occur in animals transfused through dacron wool (Swank) filters (Group DW). Even though an increase after transfusion in pulmonary Qs/Qt in Group PM did not achieve statistical significance when compared to pretransfusion Qs/Qt, it was significantly higher than that in animals in Group DW. Both filters removed considerable quantities of microaggregates; however, the polyester mesh (Pall) filters permitted passage of small microaggregates and development of detrimental physiologic changes. Dacron wool (Swank) filters completely removed measurable microaggregates and detrimental changes did not occur.

THE FORMATION of microaggregates consisting mainly of platelets and white blood cells in human blood stored under standard blood bank conditions is a well-recognized phenomenon.[1,8,11,13,17,19,26,28,30] Their presence is indicated by an elevation in screen filtration pressure (SFP) of the blood.[9–11,17,18,27,29] Transfusion of banked blood containing such microaggregates through standard blood transfusion filters may be a cause of post-traumatic pulmonary insufficiency.[8,13,15,18,20,22]

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Previous research in these laboratories has demonstrated that when blood with an elevated SFP is transfused to dogs, pulmonary artery pressure rises; arterial blood pH and O_2 consumption drop; blood pyruvate and lactate concentrations increase; pulmonary shunting of blood away from the pulmonary alveoli (Qs/Qt) increases; and diffusing capacity of the pulmonary membrane for oxygen (DO_2) decreases.[2,9] These changes are caused by embolization of transfused microaggregates to the pulmonary arterioles and capillaries and later damage to their endothelial lining may result.[2,8]

At present two principal types of micropore blood transfusion filters for removal of microaggregates from stored blood are in general use. The first contains dacron wool as its main filtering element and removes particles larger than 15 microns in diameter (Swank filter, IL 200, Extracorporeal Medical Specialties, Inc., King of Prussia, Pennsylvania). The second is a polyester mesh filter with a fixed pore size of 40 microns (Pall "Ultipore" Filter, Pall Corporation, Glen Cove, New York). It was the purpose of this study to compare the effectiveness of dacron wool (Swank) and polyester mesh (Pall) micropore blood transfusion filters in preventing the physiologic changes associated with transfusion of microaggregate-containing blood.

Materials and Methods

Using techniques previously described, blood from donor animals was collected and stored at 4 C.[9] After 5

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days SFP of each unit of blood was determined. If the SFP was elevated, the unit was then used in the study.

Mongrel dogs (average weight 15 kgs) were anesthesized with intravenous sodium pentobarbital, 25 mg/kg. Animals were ventilated on room air using a Harvard respirator at a rate of 12-14 cyles per minute and a tidal volume of 25 ± 5 cc/kg. Tidal volume was monitored using a spirometer (Wright's Respirometer Mark 12). Pancuronium bromide, 1 mg, was injected intravenously to achieve muscle relaxation and was repeated as necessary during the course of the experiment to maintain complete relaxation.

Under fluoroscopic control two catheters were passed through a right jugular venous cut-down, one into the pulmonary artery and the other into the right atrium. Using widebore catheters, the right femoral artery and vein were cannulated through a right femoral cut-down.

Each animal was allowed to stabilize and the respiratory rate and tidal volume were adjusted until femoral arterial blood studies gave stable reproducible readings for pH, P_{CO_2}, and P_{O_2}. Mixed venous P_{O_2} was then determined on blood from the right atrium. Per cent saturations of arterial and mixed venous blood were determined using an oximeter (American Optical Co.). O_2 consumption on room air was determined using an O_2 consumption meter (Oxford Instrument Co., Jackson, Mississippi).

Blood pyruvate and lactate concentrations were determined by enzymatic procedures.[21,25] Femoral artery, pulmonary artery and right atrial pressures were recorded continuously.

Percent pulmonary arteriovenous shunt (Qs/Qt) was calculated by Berggren's method.[4] Pulmonary diffusing capacity for O_2 (DO_2) was calculated by a modification of Bohr's method.[5,7,23] Ventilation: perfusion ratio (Va/Qb) was determined from the O_2-CO_2 diagram of Rahn and Fenn.[7,24]

Animals were then divided into two groups:

I. Group DW: Dacron Wool (Swank) Filter.

The blood volume of each of 7 animals was assumed to be 10% of its body weight. Each underwent an exchange transfusion of twice its calculated blood volume using the previously stored blood. Immediately prior to infusion each blood bag was warmed to 37 C in a water bath. Blood was infused in 50 cc aliquots into the femoral vein, and at the same time 50 cc aliquots were withdrawn from the femoral artery. Blood removed for the various sampling procedures was replaced during this period.

All transfused blood was passed through a dacron wool (Swank) blood transfusion filter. SFP, hematocrit and white blood cell and platelet counts were determined on each unit of blood both before and after filtration. Each blood transfusion filter was replaced after three units (1500 cc) of blood had passed through it. The average time needed to complete each exchange transfusion was 90 minutes.

Once transfusion had been completed Qs/Qt, DO_2 and Va/Qb were again determined. At the conclusion of the experiment 5 animals were sacrificed and the positions of the pulmonary artery and right atrial catheters were confirmed. The remaining two animals served as followup models. Indicated determinations were repeated 6 hours after transfusion had been completed and these latter two animals were then sacrificed.

A sample of lung tissue was obtained from 6 of the 7 animals for microscopic pathological examination. Sections of representative pieces of lung tissue were routinely stained with hematoxylin and eosin (H&E) and with periodic-acid-Schiff (PAS) and Verhoeff-Van Gieson (VVG) stains as the need arose.

II. Group PM: Polyester Mesh (Pall) Filter.

Seven animals were included in this group. Each underwent the same protocol as those in Group DW except that a polyester mesh (Pall) filter (pore size 40 microns) was used in place of the dacron wool (Swank) filter.

Results

Pretransfusion arterial blood pH, P_{CO_2} and P_{O_2} did not differ significantly between the two groups (Table 1). After transfusion pH decreased in both groups. This change was of statistical significance only in Group PM ($P<0.05$). Changes in arterial P_{CO_2} and P_{O_2} were not statistically significant in either group.

There was no significant difference between pretransfusion O_2 consumptions of both groups (Table 1). Post-transfusion O_2 consumption of Group DW did not change, but that of Group PM decreased. This change did not achieve statistical significance, but when the post-transfusion O_2 consumption in Group PM was compared with the post-transfusion O_2 consumption in Group DW, a significant reduction was noted ($P<0.025$).

Arterial blood pyruvate and lactate concentrations did not change significantly after transfusion in Group DW (Table 1). In Group PM statistically significant post-transfusion increases occurred in both pyruvate ($P<0.0125$) and lactate ($P<0.005$) concentrations.

There was no significant statistical difference between pre-transfusion Qs/Qt in the two groups (Table 1). After transfusion Qs/Qt decreased in Group DW and increased in Group PM. These latter changes were not statistically significant; however, post-transfusion Qs/Qt in Group PM was significantly higher than that in Group DW ($P<0.025$).

DO_2 in Group DW did not change significantly following transfusion (Table 1), but in Group PM, DO_2 decreased ($P<0.05$).

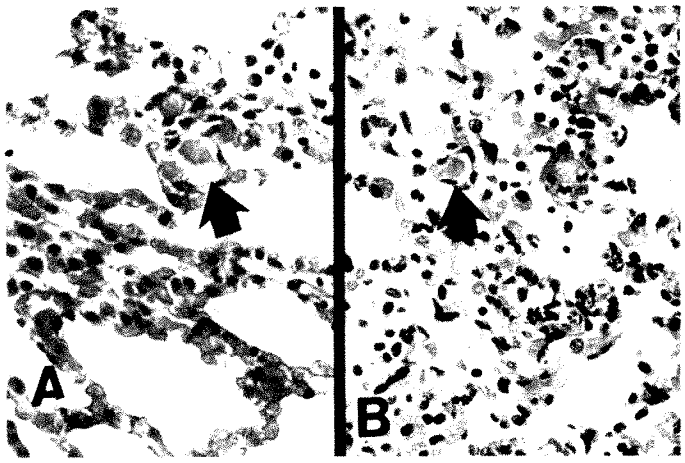

FIG. 1. Lung sections from two different dogs in Group PM showing typical findings in dogs receiving blood transfusions through polyester mesh (Pall) micropore transfusion filters. Homogenous pulmonary microemboli are seen mainly in distended alveolar capillaries (arrows). Mild alveolar cell proliferation is also present. (left) H&E, original × 390. (right) H&E, original × 320.

Changes in Va/Qb after transfusion were not statistically significant in either group and did not differ significantly between groups (Table 1).

Two animals in each group were restudied 6 hours after exchange transfusion had been completed. No change was noted to have occurred in Qs/Qt of either group since the previous determination. However DO_2 of Group PM remained lower than that of Group DW. Because of the small number of samples, the data could not be statistically analyzed.

Pulmonary artery, right atrial and femoral artery pressures did not differ significantly between groups before transfusion nor did they change significantly after transfusion.

Prior to filtration, average SFP of the blood used in Group DW was 424 mm Hg and that used in Group PM was 370 mm Hg. After dacron wool (Swank) filtration, average SFP fell to 4 mm Hg. Average SFP was 26 mm Hg after polyester mesh (Pall) filtration (comparison of average post-filtration SFP's, $P<0.005$).

Average white blood cell count and hematocrit did not change after filtration through either filter. Average platelet count dropped after dacron wool (Swank) filtration from $9.80 \pm 2.75 \times 10^4/\text{mm}^3$ to $6.12 \pm 2.16 \times 10^4/\text{mm}^3$ ($P<0.025$) and after polyester mesh (Pall) filtration from $9.92 \pm 3.28 \times 10^4$ to $9.78 \pm 3.23 \times 10^4$ ($P>0.05$).

In the lungs of 5 of the 6 animals studied in Group DW, the pulmonary microcirculation was free of emboli. In the other only a single isolated homogenous embolus was found in a distended alveolar capillary and the alveolar spaces were free of edema and exudate.

Lung sections from 5 of the 6 dogs studied in Group PM showed emboli in the pulmonary circulation (Fig. 1). In 4 dogs microemboli were homogenous, PAS positive and scattered mainly in the alveolar capillaries with an occasional embolus distending a precapillary arteriole. Another of these dogs had an embolus in a branch of the pulmonary artery at the level of the respiratory bronchiole.

Discussion

Because of the rapid flow rates allowed and their ability to remove gross blood clots, standard blood transfusion filters (pore size 170 microns) achieved widespread clinical acceptance in the middle 1950's. It has been recognized for some time that when these filters are used during blood transfusion, they allow varying amounts of amorphous particles that may be present in the blood to pass into the recipient's circulation.[16] Until recently such material was not thought to be harmful. The possibility that microaggregates in banked blood may be related to the development of pulmonary insufficiency has focused attention on the importance of these particles and the inadequacy of this type of blood transfusion filter in their removal.[2,3,8,9,13,15,20,22,28]

In 1961 Swank found that filtration of blood through packed dacron wool removed large numbers of microaggregates and caused a reduction to normal of SFP of stored blood.[28] In 1964 Jenevein et al. found emboli in the pulmonary arterioles and capillaries of patients who died after receiving large numbers of blood transfusions.[13]

TABLE 1. *Comparison of Dacron Wool (Swank) and Polyester Mesh (Pall) Filters In Prevention of Pulmonary Microembolism.*

	Group DW		Group PM	
	Pretx.	Posttx.	Pretx.	Posttx.
Arterial blood pH	7.40 ±0.03	7.33 ±0.02	7.37 ±0.02	7.19 ±0.16
P_{CO_2}, mm Hg	29 ±8	26 ±2	32 ±4	36 ±7
P_{O_2}, mm Hg	102 ±4.7	103 ±8.6	103 ±47	107 ±14.7
O_2 consumption, ml/min.	84 ±9	83 ±8	82 ±11	71 ±10
Blood pyruvate, mg%	2.2 ±0.5	1.9 ±1.2	1.1 ±0.4	2.1 ±0.7
Blood lactate, mg%	27 ±8.0	35 ±12.0	15 ±6.0	53 ±26
Qs/Qt, %	10 ±3	8 ±2	12 ±3	14 ±6
DO_2, ml/min/mm Hg	6.1 ±2.6	5.8 ±3.7	5.1 ±0.8	3.4 ±0.9
Va/Qb	1.5 ±0.4	1.3 ±0.3	1.0 ±0.2	1.1 ±0.2
Average SFP of transfused blood, mm Hg:				
Before filtration	424		370	
After filtration	4		26	

Later McNamara et al. demonstrated that arterial hypoxemia occurred in combat casualties receiving at least 10 units of blood each,[18] and pulmonary changes were also demonstrated in combat casualties who died shortly after resuscitation.[15,20]

In 1970 a new dacron wool blood filter for use in open heart surgery was introduced.[12] Initial use of this filter in the extracorporeal circuit was associated with a reduction in hospital mortality rate for open heart procedures from 19.8% to 6.5%, and in the incidence of occurrence of cerebral non-fat emboli from 31% to 4.1%. Because of these dramatic results several types of smaller micropore filters have recently been prepared for use during blood transfusion. Those most widely used are the dacron wool (Swank) and the polyester mesh (Pall) filters.

The dacron wool (Swank) blood transfusion filter is composed of two filtering elements (Fig. 2). The upper part is a nylon mesh clot filter (pore size 250 microns). The lower part consists of packed dacron wool followed in sequence by another nylon mesh filter (pore size 200 microns). The dacron wool serves as the effective filtering element and appears to remove microaggregates by providing a large surface to which the particles may adhere. The various filter components are enclosed in an outer polycarbonate body measuring 12 x 4 cm with a maximum diameter of 4 cm. After filtration is completed, residual blood volume in the filter is 50 cc.

It may be postulated that when blood is infused under pressure through dacron wool transfusion filters, compression of the dacron wool fibers might occur and flow rate thereby be reduced. If the pressure were subsequently removed from the filter, the dacron wool might re-expand and release a variable number of contained microaggregates—the so-called "unloading effect." Experiments in this laboratory have substantiated that such an effect does not occur. Furthermore, at least three, and probably four, units of unexpired human blood with an elevated SFP can be filtered through a dacron wool (Swank) blood transfusion filter either by gravity or under pressure without causing an elevation in post-filtration SFP and before the filter occludes with microaggregates.[14]

The polyester mesh (Pall) filter functions on a principle completely different from the dacron wool (Swank) filter (Fig. 3). The main filtering element is a polyester mesh with a uniform pore size of 40 microns. The mesh is arranged in a pleated accordion-like manner in juxtaposition to and immediately following a larger mesh filter (pore size 1.25 mm). The entire apparatus is enclosed in a rigid outer polypropylene body. Total filtration surface area is 160 cm² and negligible residual volume remains in the filter after transfusion is completed. In general, the polyester mesh filter will allow about 7 units of unexpired whole human blood to pass before filter flow ceases.

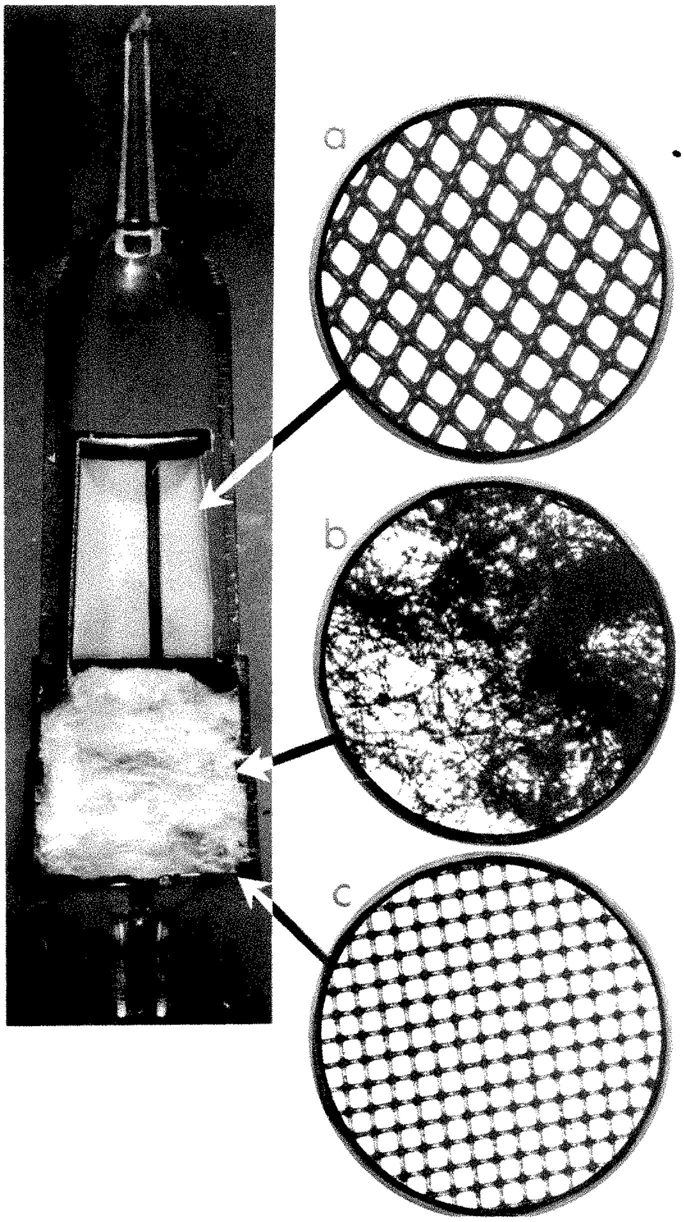

FIG. 2. Dacron wool (Swank) micropore blood transfusion filter. Cut-section demonstrates upper (a) nylon mesh clot screen (pore size 250 microns) followed in sequence by (b) packed dacron wool and another (c) nylon mesh filter (pore size 200 microns). The upper spike of the polycarbonate body is inserted directly into the transfusion container and a standard intravenous set into the lower outlet port.

In this research comparison of data revealed no statistically significant differences between pre-transfusion pH, O_2 consumptions and Qs/Qt for animals transfused through dacron wool (Swank) filters and those transfused through polyester mesh (Pall) filters. Comparison with post-transfusion values revealed a significant decrease in pH in Group PM ($P<0.05$) but no statistically significant changes in the other measurements. However, when the post-transfusion values for Group PM were compared with the post-transfusion values for Group DW, statistically significant differences were noted in all of these

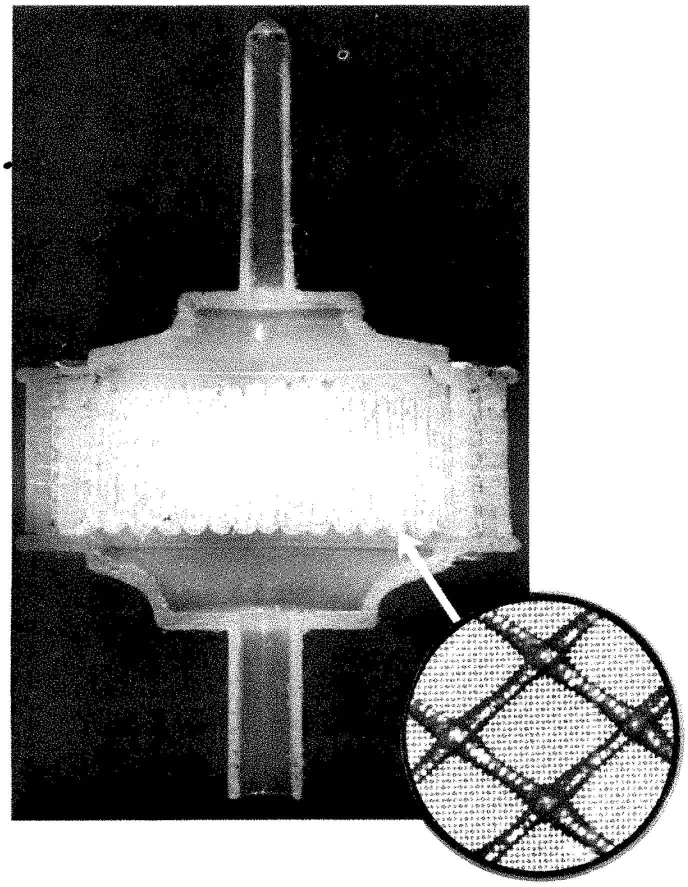

FIG. 3. Polyester mesh (Pall) micropore blood transfusion filter. Cut-section demonstrates polyester mesh (pore size 40 microns) supported in accordion-like fashion and immediately following a larger mesh filter (pore size 1.25 mm). The upper spike of the polypropylene body is inserted directly into the transfusion container and a standard intravenous set into the lower outlet port.

parameters. In addition DO_2 decreased significantly after transfusion in Group PM. These comparisons appear to indicate that while the polyester mesh (Pall) filter offered significant protection against induction of detrimental changes, such protection was not complete and a greater degree of protection was provided by the dacron wool (Swank) blood filter.

In unpublished research performed in these laboratories using 24 units of unexpired human blood, the normal range for SFP of human blood was found to be 7 ± 4 mm Hg. In the present experiments the highly significant difference between the post-filtration SFP of the blood filtered through the polyester mesh (26 mm Hg) and that filtered through the dacron wool filters (4 mm Hg) ($P<0.005$) indicates that varying numbers of microaggregates passed the polyester mesh (Pall) filter.

This was verified by the pathologic examinations performed on the lungs of the 6 animals in each group. Significantly, multiple pulmonary microemboli were noted in 5 of the 6 animals transfused through the polyester mesh (Pall) filters and in none of those transfused through the dacron wool (Swank) filters. That these small microemboli were of pathologic import was further confirmed not only by the detrimental alterations in pulmonary physiology noted in animals transfused through the polyester mesh (Pall) filters but also by the absence of such changes in those transfused through the dacron wool (Swank) filters.

The ultimate fate of pulmonary microemboli administered during blood transfusion is unclear. Transfused microaggregates may break down in the capillaries and release their organelles to the surrounding tissue.[8] Lysosomal granules are known to contain lytic enzymes capable of tissue digestion, and their breakdown may well be a mechanism whereby endothelial damage, such as that seen in post-traumatic pulmonary insufficiency, is produced.

Particles in the 40 micron size range and smaller can pass through the pores of the polyester mesh (Pall) filter, but are removed by the dacron wool (Swank) filter.[27] There would appear to be little reason to believe that these particles, as well as those of larger size, are not capable of causing these same sorts of alterations. While the early pathophysiologic significance of these small particles was demonstrated in the present research, possible longer term effects have not yet been defined.

Passage of blood through either the dacron wool (Swank) or polyester mesh (Pall) filter led to a reduction in platelet count. Since microaggregates consist mainly of platelets, this is not surprising. That this reduction achieved statistical significance in those specimens filtered through the dacron wool (Swank) filter but not in those filtered through the polyester mesh (Pall) filter further confirms the increased removal of microaggregates by the former filter compared to the latter.

Platelets in whole blood stored for 5 days at 4 C are not considered to be biologically active.[1,6,30] Nevertheless, the effectiveness of dacron wool blood filtration in removing microaggregates from stored blood appears to be proportionate to the adhesiveness of the platelets. It is those aggregated platelets with increased adhesiveness and decreased viability that are removed.

This research should have direct and immediate clinical applicability. Because of the increasingly widespread use of micropore blood transfusion filters, these experiments were designed to compare in vivo the effectiveness of the two most widely used micropore filters in preventing pulmonary microembolism. Both the dacron wool (Swank) and polyester mesh (Pall) filters removed considerable quantities of microaggregates during transfusion. However, the polyester mesh (Pall) filters did not remove small aggregates.

The data indicate that such particles are of pathophysiologic significance. Their accumulation in large numbers might well lead to the development of detrimental pulmonary abnormalities. Even though particle removal by polyester mesh (Pall) filters was only partial, the use of these filters rather than standard blood transfusion filters should allow administration of much larger quantities of blood before such changes become manifest.

It may be possible to pass greater volumes of blood through the polyester mesh (Pall) filter than through the dacron wool (Swank) filter before the filter becomes occluded, but this increased passage is at the expense of permitting administration of small microaggregates. Microaggregate administration during blood transfusion can be completely prevented by determination prior to transfusion that SFP of the blood is normal or by administration of the blood through dacron wool (Swank) blood transfusion filters.

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Renal Artery and Vein Injury Following Blunt Trauma

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Blunt injuries of the renal vascular pedicle occur infrequently. The experience with fourteen cases of blunt renal vascular trauma is presented. Most patients were injured in motor vehicle accidents. The diagnosis was made immediately after admission in 6 patients, delayed in 5, and at autopsy in 3. Most patients presented with gross or microscopic hematuria. The diagnosis of renal vascular injury was suggested by IVP in most instances. Surgical management was used in the 6 patients in whom the immediate diagnosis of renal pedicle injury was made: primary vascular repair was carried out in 4 patients and nephrectomy in two. Conservative management was used in 4 of the 5 patients with delayed diagnosis, and nephrectomy was required in the fifth. Three patients received no treatment as two were dead on arrival and one died during laparotomy. Seven patients died (50%). One of the 7 survivors has a functioning kidney following repair of a renal vein laceration. Three patients with devascularized kidneys have been followed long term and have not developed hypertension. An IVP should be mandatory following severe blunt trauma, especially when hematuria is present. Renal arteriography is indicated with distortion of calyces, extravasation or nonfunction seen on IVP and allows a definitive diagnosis of renal vessel injury to be made.

ALTHOUGH BLUNT INJURIES of the renal pedicle occur infrequently, loss of renal tissue results unless there is restoration of blood flow. Approximately 30 cases have been reported in the literature. The immediate diagnosis and management of these lesions is mandatory if preservation of renal tissue is to be achieved. This report records the experience with blunt renal vascular injuries in fourteen patients.

Material

Between January, 1959 and June, 1974, 466 patients were treated for renal injuries. Fourteen of these had blunt renal vascular trauma.

The presence of gross or microscopic hematuria on admission, or the finding of retroperitoneal or perinephric hematoma at laparotomy were the indications for infusion IVP. When distortion of the calyces, extravasation or non-function was demonstrated on IVP, selective renal arteriography was performed. Arteriography was omitted in favor of renal exploration when these radiographic findings were seen on IVP performed during laparotomy. Exploration of the kidney was accomplished after control of the renal vessels was acquired.

Surgical management of these injuries was only carried out since 1968.

Results

Age and Sex

The ages of patients ranged from 2 to 74 years. Six patients were under 20 years of age and 4 patients were in the 20-40 year group. There were 9 males and 5 females.

Type and Site of Injury

Eleven patients were involved in traffic accidents: 8 as automobile passengers and three were pedestrians. One patient was injured in a skiing accident, one as a result of a child beating and one due to a crush injury by a steam shovel.

The most common injury was renal artery thrombosis which occurred in 5 patients. Renal artery laceration occurred in 4 and renal vein laceration in 4 patients. One

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TABLE I. *Management and Results of Renal Vessel Injury*

Sex, Age	Site & Type of Injury	Associated Injuries	Delay in Diagnosis	Management	Followup IVP on Side of Injury
M, 35	Rt. vein laceration	Fracture femur, tibia, ankle, pelvis	None	Repair	Normal 7 mos
F, 17	Rt. artery laceration	Ruptured liver	None	Repair	Non-function 1 yr
M, 23	Lt. artery laceration	Ruptured colon	None	Repair	Died from assoc. inj.
F, 17	Rt. vein laceration	Ruptured diaphragm, liver, colon, Hemothorax fractured tibia, radius. Head injury	None	Repair	Died from assoc. inj.
F, 52	Lt. vein laceration	Ruptured spleen Subdural hematoma	None	Nephrectomy	——
F, 74	Rt. artery thrombosis	Ruptured diaphragm, spleen, small bowel	None	Nephrectomy	Died from assoc. inj.
M, 16	Rt. artery thrombosis	Abdominal wall avulsion	12 hrs	Conservative	Non-function 8 yrs
M, 2	Rt. artery laceration	Abdominal bowel infarction	12 hrs	Delayed Nephrectomy	Died from assoc. inj.
F, 19	Rt. artery thrombosis	Ruptured liver	24 hrs	Conservative	Non-function 5 yrs
M, 36	Lt. artery thrombosis	Ruptured liver, spleen	24 hrs	Conservative → Delayed Nephrectomy	——
M, 21	Lt. artery thrombosis	Fracture lumbar vert.	3 yrs	Conservative	Non-function 6 yrs
M, 48	Rt. artery and vein laceration	Ruptured aorta, bowel, liver, spleen, ureter. Subdural hematoma	D.O.A.	——	——
M, 57	Rt. vein laceration	Ruptured liver, colon, ileac artery. Head injury	D.O.A.	——	——
M, 17	Rt. artery laceration	Ruptured liver, spleen. Head injury	Died in O.R.	——	——

patient suffered laceration of both the renal artery and vein (Table 1).

Diagnosis

The diagnosis was made immediately after admission in 6 patients, delayed in 5 and at autopsy in 3 (Table 1).

With immediate diagnosis hematuria was present in 5 (gross in 3 and microscopic in 2) and not recorded in the sixth patient. An infusion IVP revealed unilateral non-function in 3, extravasation in one and poor visualization in two patients.

The diagnosis was delayed 12 hours after admission in two patients, 24 hours in two and 3 years in the remaining patient. Hematuria was present in three (gross in one and microscopic in 2) and not known in 2 patients. An infusion IVP revealed non-function in 4 and was not performed in one patient in whom the diagnosis was made at a 12-hour delayed laparotomy for associated visceral injuries.

The patient with a 3-year delay had recurrent urinary tract infections and had a history of being in an automobile accident 3 years previously, at which time he sustained a lumbar vertebral fracture and had microscopic hermturia which cleared over several days. Aside from several urinary tract infections the patient had had no other difficulties since the accident. Non-function of the left kidney was demonstrated on an IVP done for the workup of his recurrent urinary tract infections. Arteriography showed an abrupt cutoff 5 mm beyond the origin of the left renal artery.

The diagnosis was made at autopsy in two patients admitted dead on arrival and in one patient who died on the operating room table after an infusion IVP had shown non-function of the left kidney.

Associated Injuries

Associated injuries were present in all 14 patients. The patients had an average of 3 major injuries. Twelve had intra-abdominal injuries. The intra-abdominal injuries were: 6 liver lacerations, 6 bowel ruptures, 5 ruptured spleens, and 2 ruptured diaphragms. Associated injuries were responsible for the death of 7 patients.

Treatment

Surgical management was used in the 6 patients in whom immediate diagnosis of renal pedicle injury was made. Primary vascular repair was carried out in 4 and nephrectomy in 2 patients. Two patients having primary vascular repair and one patient having a nephrectomy died from the associated injuries in the postoperative period.

Conservative management was used in 4 of the 5 patients with the delayed diagnosis of renal pedicle injury. The fifth patient had a nephrectomy at the time of a 12-hour delayed laparotomy for associated visceral injuries and died from these associated injuries in the postoperative period. One of the 4 patients managed conservatively required a nephrectomy for persistent retroperitoneal hemorrhage.

Three patients had no treatment as two were dead on

TABLE 2. *Associated Injuries with Renal Pedicle Trauma*

Liver laceration	6
Rupture of small or large bowel	6
Severe closed head injury	5
Ruptured spleen	5
Ruptured diaphragm	2
Rupture of the thoracic aorta	1
Extremity fracture	5
Lumbar fracture	1
Abdominal wall avulsion	1

arrival and one died on the operating table from associated injuries.

Followup

Seven patients (50%) survived and were discharged from the hospital; 2 following primary vascular repair, 2 following nephrectomy (one immediate and one late) and 3 managed conservatively.

One primary repair of a renal artery failed as shown by non-function on a followup IVP. The patient has been observed for one year and has developed no symptoms or signs. The other primary repair of a renal vein has been successful for 7 months with normal function on postoperative IVP.

The three patients with devascularized kidneys managed conservatively have been followed for 5, 6 and 8 years so far with no return of function as shown by IVP. Hypertension has not developed but one patient had 3 lower urinary tract infections.

Discussion

The kidney salvage rate is low with blunt renal pedicle injuries. This results from A) the late diagnosis of renal pedicle injury and B) high mortality rate due to the frequent multiple, severe associated injuries.

The late diagnosis of renal pedicle injury results from the conservative management of renal injury. Following trauma the finding of hematuria or a retroperitoneal hematoma at laparotomy for associated injuries makes an infusion IVP mandatory. Renal arteriography makes the definitive diagnosis of renal pedicle injury and is indicated if the IVP demonstrates distortion of calyces, extravasation or non/function of a kidney.

Multiple severe injuries were associated with renal pedicle injuries and resulted in a 50% mortality rate. Twelve of the 14 patients had associated abdominal injuries requiring immediate laparotomy. In these cases renal arteriography should be omitted in favor or renal exploration when the IVP on the operating room table shows distortion of calyces, extravasation or non-function. The mortality rate in our series is higher than previous reports.[1-4] This appears to be due to the greater number of associated injuries in our series of patients.

Some degree of success revascularizing kidneys has been achieved with surgical repair 10-19 hours after blunt trauma with injury to the renal pedicle.[5,11] When the diagnosis of renal pedicle injury is made later than 24 hours following injury no surgical treatment is indicated unless hemorrhage, infection or hypertension ensue. We have followed 4 such patients for one to 8 years and none has developed hypertension. Careful followup is necessary because hypertension has been reported in some patients.[13]

Review of the literature on blunt renal vascular injuries[1-4,6-14] identifies the salvage of only one kidney[11] among 29 pedicle injuries (3.4%). Guerriero[5] reports 4 survivors of blunt renal vascular injuries, but only comments on followup of one patient who had hypertension and decreased renal function following revascularization of an arterial injury. Ross[10] reported a patient whose renal function returned following heminephrectomy for thrombosis of an upper pole artery.

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Prolonged Retention of Glutaraldehyde-treated Skin Allografts and Xenografts:

Immunological and Histological Studies

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Glutaraldehyde (GA)-treated skin allografts and xenografts (from mice, rats and guinea-pigs) behave in the same way as judged from retention time, gross inspection, microscopic examination, and assays for graft antigenicity. The GA-treated grafts are retained for long periods of time (an increase by more than 6-fold as compared to untreated grafts), they are tightly bound to the recipient, they are initially soft but become progressively stiffer with minimal shrinkage in size, and remain free from infection. The histology shows that the grafts are nonviable and fixed by the GA, they are avascularized but the general structure of the skin (epidermis, adnexa and dermis) is preserved for about 3 months. The antigenicity of the GA-treated grafts is very poor, actually it is undetectable. They do not elicit the formation of cytotoxic antibodies, and animals sensitized by untreated allografts retain the GA-treated allografts similarly to normal unsensitized recipients. The lack of transplantation immunity is also indicated by the fact that GA-treated isografts behave and are rejected similarly to GA-treated allografts and xenografts. Microscopic examination suggests that the mechanism of rejection of GA-treated grafts is similar to that operating in the rejection of an inert foreign body. The marked prolongation in the retention of Ga-treated skin grafts and their properties justify investigations on the applicability of these grafts in clinical practice.

IN A PREVIOUS COMMUNICATION it was shown that mice allografts treated in vitro with glutaraldehyde (GA) were retained for long periods of time with minimal shrinkage in size of the graft.[14] These observations were confirmed by Im and Simmons.[8] In both studies,[8,14] however, the mice used shared identical major histocompatibility loci and they differed at minor histocompatibility loci. The present study was designed to investigate the generality of these findings by grafting GA-treated skins across the strong H-2 histocompatibility barriers and across species. Histological features and immunological parameters were also studied in order to evaluate the mechanism for the prolonged retention of GA-treated grafts. The properties of the GA-treated grafts (retention for about two months, preservation of the skin structure, and the lack of infection) justify investigation of the clinical use of these grafts.

Materials and Methods

Aqueous solution of 25% (w/v) of glutaraldehyde (GA)* and sterile solutions of 0.01 M sodium phosphate buffer (pH 7.4) - 0.15 M sodium chloride (PBS) were used.

The inbred strains employed in grafting experiments were C57BL/6 ($H\text{-}2^b$) and BALB/c ($H\text{-}2^d$) mice weighing 25-30 g, Lewis (150-200 g) and Brown Norway (BN) (100-120 g) rats which differ at major and minor histocompatibility loci,[10] and guinea pigs of the N13 strain (300-350 g). The animals were obtained from the Experimental Animal Unit, The Weizmann Institute of Science.

Full-thickness skin grafts were performed according to Billingham and Medawar.[4] Grafts were protected by vaseline gauze and plaster jackets, which were removed 10 days after transplantation. Grafts were inspected daily until they were rejected. When grafts were still retained on the host at the last inspection, the retention time was indicated with an "over" symbol (>). In the control (untreated grafts) and experimental (GA-treated grafts) groups the course of graft rejection was different. In the

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*From Sigma, St. Louis, Missouri.

TABLE 1. *Prolonged Retention of Glutaraldehyde-treated Skin Grafts.*

Group	Donor*	Recipient	Graft treatment	No. of animals	Retention time (days)	
					Average	Range
Allografts						
A	BA	C57	none	26	12.9	(11- 16)
			GA	22	>108	(29- >135)
B	C57	BA	none	17	13.6	(11- 17)
			GA	16	> 63	(37- >70)
C	BN	Le	none	13	14.3	(13- 16)
			GA	16	> 91	(55- >130)
Xenografts						
D	C57	Le	none	17	10.5	(10- 12)
			GA	19	>106	(55- >130)
E	GP	Le	none	9	15.3	(14- 18)
			GA	12	>105	(62- >130)
F	BN	C57	none	9	16.1	(15- 18)
			GA	13	> 82	(28- >120)
Isografts						
G	C57	C57	none	12	>130	(>130)
			GA	13	>120	(88- >130)
H	BA	BA	none	11	>130	(>130)
			GA	9	>104	(58- >130)
I	Le	Le	none	7	>130	(>130)
			GA	10	>103	(62- >130)

*Abbreviation for animals are: BA, BALB/c mice; C57, C57BL/6 mice; BN, Brown Norway rats; Le, Lewis rats; GP, guinea pigs of the N13 strain.

controls, survival end point was considered when about 80% of the graft was necrotic and macerated. In the experimental groups rejection was considered when about 70% of the graft was detached from the recipient bed.

Skin grafts (about 1.5 cm in diameter) were excised from the donor animal, treated in vitro, and then applied to the dorsum of the recipient. Twelve skin patches were placed in a glass vessel containing 30 ml of 3 mg/ml of GA in PBS, and kept at room temperature for 20 min with gentle manual shaking to prevent clumping. The grafts were freed from the GA by washing 4 times in 50 ml PBS. In every experiment fresh GA solution was prepared by adding 0.36 ml of GA (25% w/v) to 29.6 ml of PBS. In the control groups the grafts were exposed only to PBS.

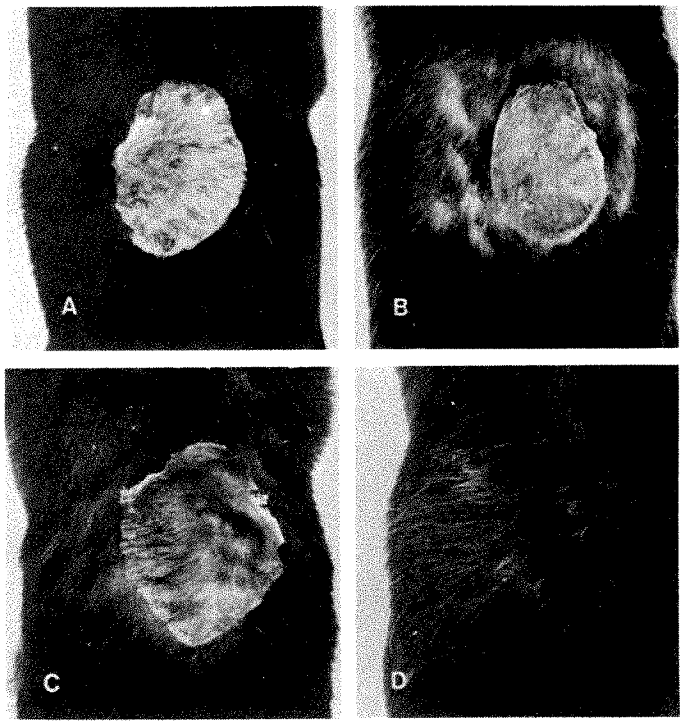

FIG. 1. Skin grafts on C57BL/6 mice at 100 days. (A), GA-treated allograft from BALB/c mouse; (B), GA-treated xenograft from BN rat; (C), GA-treated isograft; (D) untreated isograft.

The complement dependent cytotoxic antibodies in the recipients of C57BL/6 grafts were measured by the ^{51}Cr release assay (13). The ascites tumor cell EL-4, maintained in the syngeneic C57BL/6 mice, served as target cells.[5] The ^{51}Cr released by 4 times freeze-thaw of the labeled EL-4 target cells was taken as the maximum released (100%). In control experiments the sera without added complement were not cytotoxic, and they did not have anticomplementary activity.

Histological sections were stained with hematoxylin and eosin.

Results

The rejection of untreated allografts and xenografts in 6 different control groups (Table 1) occurred within a short period of time (11 to 16 days). It involved shrinkage of the skin-graft, maceration and serum exudation with slough formation.

The pattern of rejection of GA-treated skin grafts was the same in three allogeneic and three xenogeneic combinations. About half of the GA-treated grafts were retained on the host for over 100 days (Table 1, Fig. 1). After removal of the cast (day 10) all grafts were soft and pliable. However, 2-6 days later they began to stiffen, but small soft areas persisted for a long period of time. The GA-treated grafts were firmly adherent to the bed (Fig. 2). In contrast to the untreated grafts, the GA-treated grafts retained their original size (Fig. 1), and only towards the end showed some diminution in size. The rejection process was characterized by progressive desiccation of the graft, and undermining of the GA-treated graft by the host epidermis. Separation started at peripheral portions of the graft and proceeded in a continuous fashion. Occasionally, by the end of this process a dry graft having its original dimension was detached in one piece from the host. Concurrently with the graft separation, the recipient bed was found to be healed and did not expose a denuded surface. At all stages neither infection nor inflammation was observed.

In order to gain some information on the mechanism of rejection of GA-treated grafts, the effect of GA on isografts was studied. The untreated isografts in two strains of mice and in Lewis rats were soft, and survived indefinitely with normal hair growth, as expected. On the other hand, the GA-treated isografts became stiff and were rejected in a pattern which was indistinguishable from that of GA-treated allografts and xenografts (Table 1, Fig. 1). These results indicated that an immune process was not involved in the rejection of GA-treated grafts.

The sera of BALB/c mice receiving C57BL/6 allografts contained cytotoxic antibodies to C57BL/6 cells, as expected.[5] On the other hand, these antibodies were undetectable in the sera of BALB/c mice grafted with GA-treated skins of C57BL/6 mice (Fig. 3). Similar results were obtained with Lewis rats receiving untreated and GA-treated xenografts from C57BL/6 mice. These experiments show that the humoral immune response towards allografts and xenografts was not elicited upon challenging the recipients with GA-treated skins.

It is known that in addition to cytotoxic antibodies, sensitized lymphocytes are also involved in graft rejection.[5] To gain information on the cellular component we grafted 12 Lewis rats simultaneously with untreated and GA-treated skin allografts from BN rats. It was found that the average retention time of the untreated grafts was 13.6 days (range 12-15 days), while with the GA-treated grafts it was > 98 days (range 66—> 135 days). These values are similar to those determined in Lewis rats receiving either allograft separately (see Table 1). The pattern of allograft rejection was also identical in the doubly and singly grafted rats. Similar results were obtained with mice. In C57BL/6 recipients (16 mice) the first set of untreated allografts from BALB/c donors was rejected after 12.1 days (range, 10-15 days). At 20 days (counting from the first grafting) the C57BL/6 mice received a second set of GA-treated BALB/c allografts which had an average retention time of >99 days (range, 35—>130 days). Thus, in rats and mice sensitized by untreated allografts there was no demonstrable change in the retention time and in the pattern of rejection of GA-treated allografts.

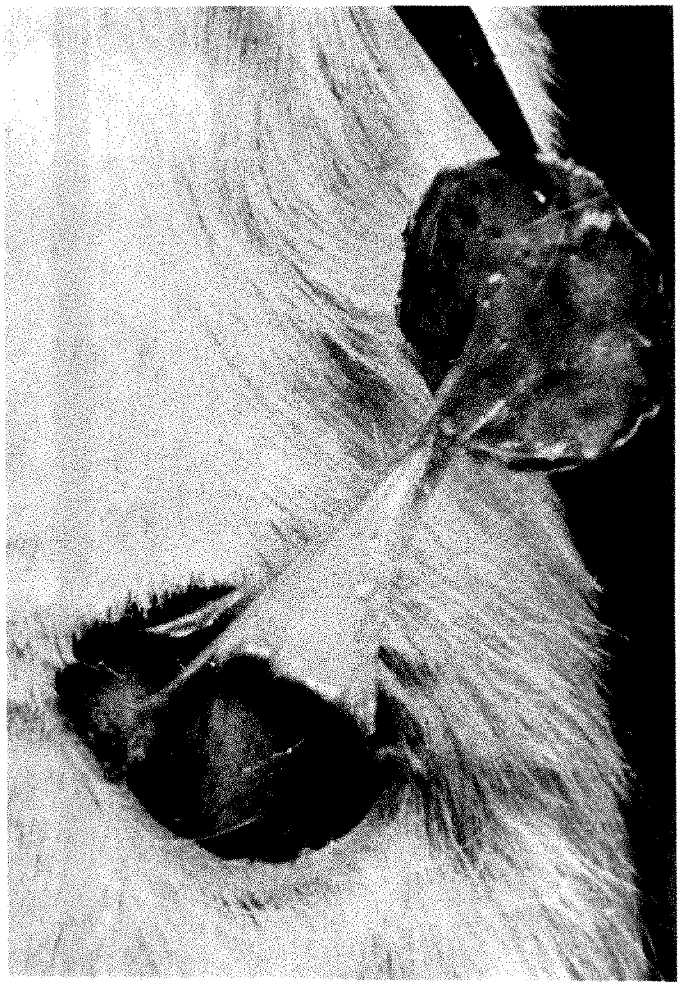

FIG. 2. The attachment of GA-treated N13 guinea pig xenograft to the bed of Lewis rat at 62 days. The xenograft was removed mechanically to demonstrate the adherence by connective tissue elements. The graft bed was free from infection.

By microscopic examination the GA-treated isografts, allografts and xenografts showed the same histological features. The characteristic findings were the preservation of the general structure of the skin over a long period of time, cellular infiltrate which subsided in the course of time, adherence of the graft to the bed by fibrillar elements, and the proliferation of blood vessels in the bed of the graft with the lack of vascularization within the graft. After 2 weeks the untreated allografts and xenografts were necrotic (epidermis and adnexa were not discernible) and heavily infiltrated by cells; subsequently the open wound healed and was covered by host epidermis. On the other hand, at 20-38 days, in the GA-treated grafts the general architecture of the epidermis and adnexa was preserved, yet the nuclei were pyknotic in many cells.

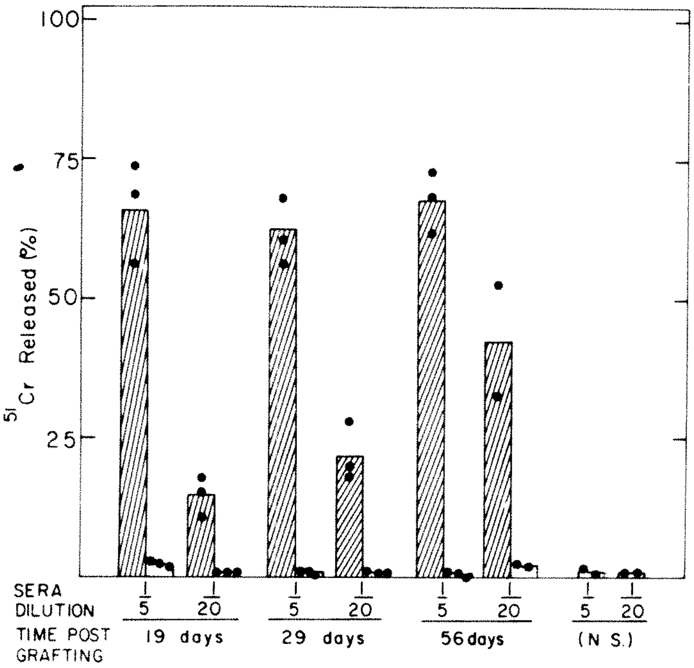

FIG. 3. Cytotoxic antibodies in the sera of BALB/c mice receiving untreated (hatched columns) and GA-treated (open columns) skin allografts from C57BL/6 mice donors. (N.S.) represent normal sera from BALC/c mice without any graft. Each filled circle represents serum from a single mouse. The target cells were the ^{51}Cr-labeled EL-4 cells.

Cellular infiltrate was mainly around the adnexa and at the graft-bed junction. The graft bed contained varying degree of infiltrate (mainly mononuclear cells) with many blood vessels which reached to the graft junction but did not penetrate it. At 90-130 days the infiltrate within the graft and bed was considerably reduced. The general structure of the graft was retained in many places, in fact it was more prominent than at earlier stages because of paucity of cellular infiltrate. The graft proper remained avascular and connection to the bed was still intact in many places (Fig. 4). In Lewis recipients, mononuclear and multinucleated giant-cells surrounded remnants of GA-treated allografts and xenografts in a manner reminiscent of the reaction towards inert foreign bodies.

The GA-treated grafts are nonviable. This is evident from the gross appearance of the grafts, their hard consistency and from the absence of vascularization.

Discussion

The studies aimed to prolong graft retention by *in vitro* treatment with GA were based on the hypothesis that GA may directly and covalently bind to the histocompatibility antigen molecules or in their close vicinity. In consequence the histocompatibility antigens would be masked and become inaccessible to the immune apparatus of the recipient.[14] This may be analogous to the situation where the coupling of long polyalanine chains to protein carrier have led to a considerable diminution in the immune response towards the protein moiety.[3] Experiments with mice which differed at minor histocompatibility loci showed that GA-treated allografts had prolonged retention time.[8,14] The data presented here demonstrated that this is also true for GA-treated allografts applied across major histocompatibility barriers and for GA-treated xenografts (Table 1).

The antigenicity of the GA-treated allografts and xenografts is markedly diminished. They did not elicit the formation of cytotoxic antibodies (Fig. 3) and sensitization of the hosts with untreated allografts did not affect the course and the prolonged retention of the GA- treated allografts (see Results). These findings confirm previous observations on the reduced antigenicity of grafts rendered nonviable by cyanide,[7] by formalin[11] or by freeze-drying.[1]

The rejection of the GA-treated grafts was characterized by progressive dessication of the graft with slow separation from the host bed. The data quoted above indicate that an immune response against the GA-treated grafts was not involved in the rejection process. The abundance of mononuclear cells and of giant-cells in the graft's bed suggest that the mechanism of rejection is similar to that operating in the reaction towards an inert foreign body.

Glutaraldehyde is a bifunctional reagent capable of reacting rapidly in aqueous solutions with the ϵ-amino group of lysine and with the α-amino groups of amino acids. These properties make it an efficient reagent for the cross-linking of proteins[2,12] which can be hardly degraded by proteolytic enzymes. It seems therefore that the GA-treated grafts remained free from infection throughout the long period of observation because the skin constituents were cross-linked by the GA. To explore this point we are currently testing the susceptibility of GA-treated skins to infestation by bacteria. The preliminary results show that GA kills bacteria commonly present on skin. Furthermore, when exposed to increasing concentrations of different bacteria (e.g. staphylococci, pseudomonas), the bacterial concentration required to initiate minor infestation of GA-treated skins is 10,000-fold higher than the concentration capable of inducing massive infestation of untreated skins.[8]

The GA-treated grafts are nonviable, yet not all dead grafts are alike. The retention of freeze-dried grafts was extended from 10 to 13 days.[1] No extention was observed in cyanide-treated allografts, and they shrank more rapidly than viable untreated allografts.[7] On the other hand, with GA-treated grafts the retention time was much more prolonged (Table 1) with minimal diminution in size (Fig. 1). The fixation by the GA is such that the general structure of the skin (epidermis, adnexa and dermis) is preserved for long periods (Fig. 4). It is avascularized but serves as a good substrate for the penetration of connec-

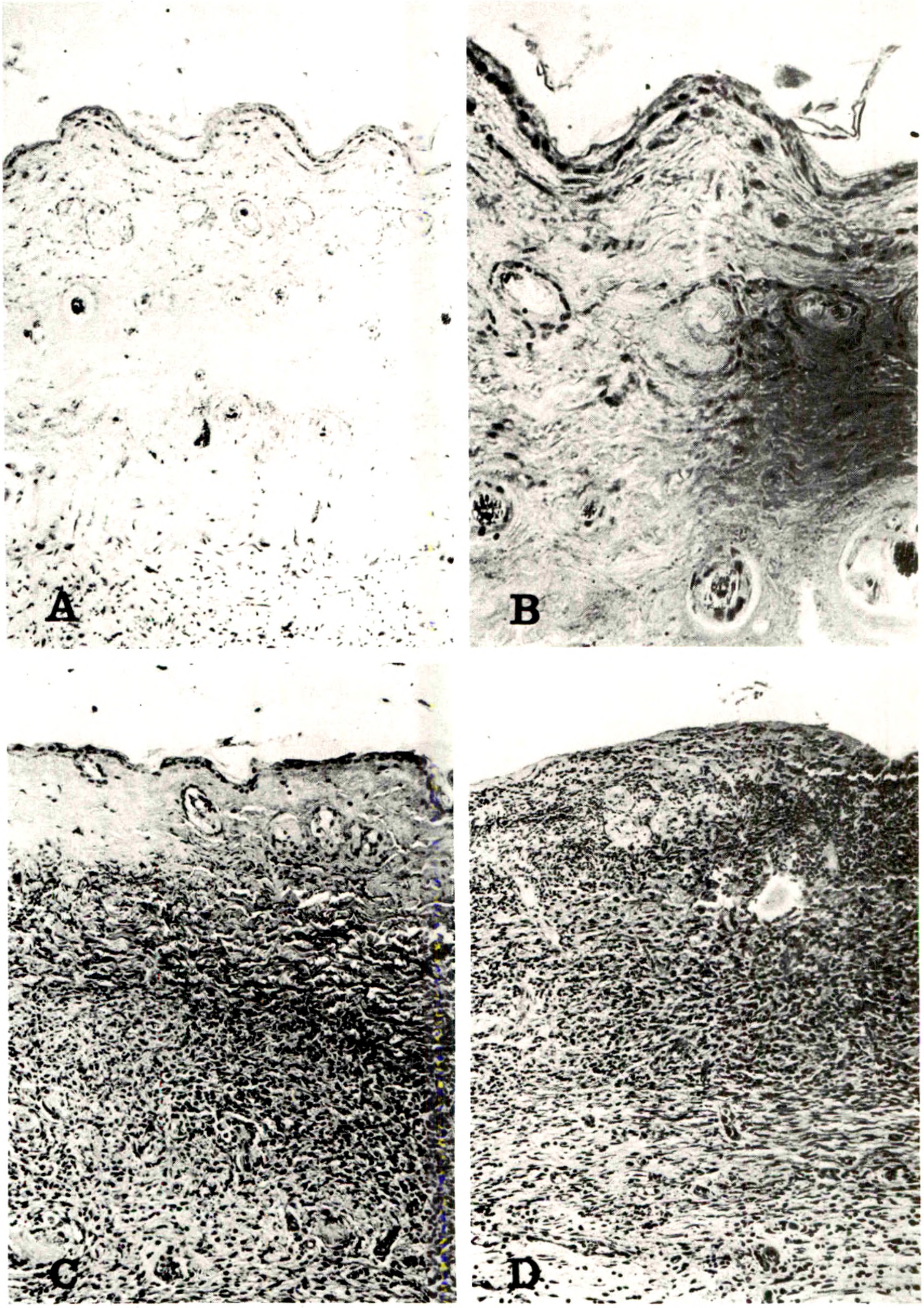

FIG. 4. Histology of xenografts. GA-treated skin from BN rat donor onto C57BL/6 mouse recipient at 92 days: A (x40); B (x100). Skin grafts from C57BL/6 mice onto Lewis rats: GA-treated at 37 days (C, x40); untreated at 14 days (D, x40). The GA-treated xenografts (A,B,C) are avascularized, the epithelial elements are preserved, and they contain cellular infiltrates (mainly mononuclear cells) which decrease with time. At 37 days the bed contains many small and medium sized blood vessels. The untreated xenograft (D) is destroyed and heavily infiltrated.

tive tissue fibers which keep it closely adherent to the recipient (Fig. 2), and granulation tissue develops at the wound bed.

The marked prolongation in retention times and the properties of GA-treated grafts prompted us to evaluate their clinical applicability. Indeed, the use of GA-treated skin allografts for the treatment of burned patients,[15] and of GA-treated umbilical cord veins for arterial substitutions in humans[6] have given encouraging initial results. The findings that in animals GA-treated allografts and xenografts behave in the same way are relevant for the clinical trials. They suggest that it would be possible to overcome the difficulties encountered in the limited supply of skin (or other organs) from human sources by using GA-treated xenografts in clinical practice.

Acknowledgment

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Postoperative Arterial Blood Gas Measurement in Obese Patients:

Effect of Position on Gas Exchange

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The effect of position change on blood gas exchange was studied in 22 markedly obese, otherwise healthy, women both preoperatively and postoperatively. There was a statistically significant decrease in arterial oxygen tension and a simultaneous reduction both in the arterial carbon dioxide tension and the base excess with the assumption of the supine versus the semirecumbent position on postoperative days one and two. However, no positional difference was demonstrable in any variable by the third postoperative day. This study indicates that in obese patients during the first 48 hours after abdominal surgery, assumption and maintenance of the semirecumbent posture is a valuable therapeutic adjunct to improve arterial oxygenation.

THE OVERALL INCIDENCE of postoperative pulmonary complications, and hence hypoxemia, is affected by age, sex, duration of the operation, body habitus, preexisting pulmonary disease, and cigarette smoking.[8] Obese subjects undergoing abdominal surgery are recognized as being a particularly high risk group in terms of postoperative pulmonary complications.[3] Recently we demonstrated that markedly obese subjects, after jejunoileal small bowel bypass, manifest significant hypoxemia during the first four postoperative days.[14] We have also shown that with vertical incisions the hypoxemia was more marked than with transverse incisions.[15] Postoperatively, patients are usually placed in the supine position. Such a position, however, may further increase the severity of the hypoxemia because of the reduction in lung volume secondary to the pressure of the intra-abdominal contents on the diaphragm.

The purpose of the present study was to evaluate, in a group of postoperative obese females, whether a change from the supine to the semirecumbent position would alter blood gas exchange.

Method

Twenty-two morbidly obese non-smoking female patients, without clinical evidence of cardiopulmonary disease, were studied preoperatively and on postoperative days one through three. Informed consent was obtained from each unsedated patient preoperatively. The operative incisions (vertical midline) and surgical procedures (jejuoileal bypass, liver biopsy, and appendectomy) were identical for all patients. The mean duration of anesthesia was 186 ± 23 minutes.

Samples of arterial blood were obtained with the patient in bed, breathing room air for 15 to 20 minutes. Each patient served as her own control. Sampling was performed anaerobically from the radial artery by direct puncture after infiltration of the skin with 0.5% lidocaine or from an indwelling intra-arterial cannula. Arterial blood was collected into iced plastic syringes containing heparin and analyzed for P_{O_2}, P_{CO_2}, and pH, within 30 min of sampling, by the same technician in our research laboratory. Appropriate corrections were made for changes produced by time and temperature.[6]

Each arterial sample was taken at least 4 hours after any narcotic medication or respiratory therapy treatment: the specimens were obtained each morning between 8 and 10 AM.

The fractional oxygen saturation of hemoglobin $\left(\frac{HbO_2}{Hb + HbO_2}\right)$ was calculated according to the method of Thomas[12] using measured arterial pH, P_{CO_2}, P_{O_2}, and

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TABLE 1. *Physical Characteristics of 22 Obese Adult Female Subjects*

Case #	Age (Yrs.)	Height (cm)	Body Weight (kg)	Deviation from ideal weight (%)*	Weight (kg)/ Height (cm) ratio
1	27	162	154.0	192	0.95
2	27	173	156.0	153	0.90
3	37	150	116.4	146	0.78
4	33	175	128.6	103	0.73
5	31	168	125.5	116	0.75
6	24	168	155.5	168	0.93
7	38	165	141.8	154	0.86
8	36	163	128.6	137	0.79
9	38	165	190.0	240	1.15
10	39	159	150.0	188	0.94
11	34	175	142.0	124	0.81
12	30	178	178.0	173	1.00
13	52	163	118.0	117	0.73
14	27	160	104.0	97	0.65
15	47	163	160.0	195	0.98
16	31	176	125.0	97	0.71
17	25	178	154.1	136	0.87
18	29	170	131.4	120	0.77
19	42	165	125.0	124	0.76
20	26	171	119.0	99	0.70
21	42	170	128.0	114	0.75
22	29	164	104.0	86	0.63
Mean	33.8	167.3	138	140	0.82
S.D.	7.5	7.0	22.3	39.5	0.13

*Deviation from ideal weight $= \frac{\text{actual weight (kg)} - \text{ideal weight (kg)}}{\text{ideal weight (kg)}^{\dagger}} \times 100$

†Ideal weight = determined from the standard Metropolitan Life Insurance Co. weight/height table[10] using the mid-range value of the medium frame group at each height.

hematocrit. Collected data were analyzed with an analysis of variance to ascertain differences within and between the two positions studied. Subsequently, a student's paired t-test was employed to evaluate the significance of the differences between the two groups (semirecumbent versus supine).

Results

Table 1 characterizes this patient sample as young (mean age 33.8 years) and markedly obese (mean of 140% in excess of ideal weight).

Patients were studied to ascertain the effect of a positional change on arterial blood gases. There was no statistically significant difference in any blood gas measurement in the semirecumbent versus the supine position ($P > 0.05$) preoperatively (Tables 2 and 3). However, semirecumbent arterial oxygen tension (Pao_2) was reduced (mean 76.4 ± 1.6 torr) when compared to non-obese patients matched for age; assumption of the supine position slightly improved mean (Pao_2) (78.4 ± 2.4 torr), although statistically this was not significant.

There was a statistically significant increase in arterial oxygen tension, carbon dioxide tension and base excess with the assumption of the semirecumbent position on postoperative days one and two (Tables 2 and 3, Fig. 1).

At the levels of arterial oxygenation encountered postoperatively in some of these obese patients, the slope of the hemoglobin-oxygen dissociation curve can change radically. On the more vertical portion of this curve (Pao_2 $<$55 to 60 torr), a small reduction in Pao_2 will cause a marked decrease in the percent saturation of hemoglobin. Consequently, in addition to measurement of Pao_2, we compared the changes in per cent saturation of hemoglobin. These results comparing the two positions are presented in Table 2. As would be predicted from the Pao_2 values, there is a statistically significant reduction in hemoglobin saturation in the supine versus the semirecumbent position on postoperative days one and two, but not on day three.

Comparing oxygenation variables (Pao_2 and per cent saturation of hemoglobin) between postoperative days one and two, there was no statistical difference identifiable. However, the lowest values for both Pao_2 and per cent saturation of hemoglobin were noted on postoperative day two. The most profound reduction in arterial oxygenation was observed in the supine position on postoperative day two (Table 2).

The results in Table 3 demonstrate that there is a statistically significant increase in Paco_2 and base excess following the assumption of the semirecumbent postion on postoperative days one and two. However, the increase in these two variables is not clinically relevant.

TABLE 2. *Positional Differences in Arterial Oxygenation (Semirecumbent to Supine). Values Represent Mean of 22 Obese Adult Female Patients Breathing Room Air.*

Oxygenation Variable	Semirecumbent Mean ± S.E.	Semirecumbent Range	Supine Mean ± S.E.	Supine Range	Mean Difference (supine-semi-recumbent)	Significance (P value)
Preop						
Pao_2 (mm Hg)	76.4 ± 1.6	63 – 93	78.4 ± 2.4	58 – 96	2.0	N.S.*
% O_2 Saturation of Hb	95.5 ± 0.7	92.6 – 97.1	95.6 ± 0.8	89.9 – 97.8	0.1	N.S.
Postop Day 1						
Pao_2 (mm Hg)	64.2 ± 2.1	48 – 88	58.6 ± 1.8	41 – 72	−5.6	<0.001
%O_2 Saturation of Hb	92.2 ± 0.7	79.0 – 96.7	90.1 ± 0.9	76.0 – 94.5	−2.1	<0.001
Postop Day 2						
Pao_2 (mm Hg)	60.4 ± 2.1	43 – 78	54.5 ± 1.8	38 – 66	−5.9	<0.001
%O_2 Saturation of Hb	91.1 ± 0.9	77.2 – 95.8	88.5 ± 1.1	73.7 – 93.9	−2.6	<0.001
Postop Day 3						
Pao_2 (mm Hg)	61.4 ± 2.7	46 – 82	61.5 ± 2.3	46 – 80	0.1	N.S.
%O_2 Saturation of Hb	91.4 ± 0.9	78.0 – 96.5	91.7 ± 0.8	78.0 – 95.8	0.3	N.S.

*N.S. = not statistically significant using Student's *t*-test.

An attempt was made to correlate the mean difference (supine-semirecembent) in Pao_2 with age, weight/height ratio, and per cent deviation from ideal weight on postoperative days one and two. No significant correlation was found.

Discussion

Presently there are no data available relating the effect of changes in body position on arterial oxygen tension in postoperative patients, either non-obese or obese. Tucker[13] has reported the effect of change from the seated to the recumbent position on the lung volumes of obese subjects; there were significant decreases in all lung subdivisions, except the residual volume. The expiratory reserve volume, in particular, became quite small in the recumbent position.

LeBlanc et al[7] were the first to suggest the phenomenon of airway closure as a factor which might influence gas exchange with the change in posture. They pointed out that while "closing volume" (lung volume at which airway closure started to occur) does not change substantially with posture, there is a decrease in the functional residual capacity (FRC) in the supine position, thus increasing the chance of the "closing volume" falling within the breathing range. If this occurred, ventilation to affected regions would be impaired, thereby lowering the regional ventilation to perfusion (V/Q) ratios. This un-

TABLE 3. *Positional Differences in Arterial Acid-base Variables (Semirecumbent to Supine) in 22 Obese Adult Female Patients Breathing Room Air.*

Acid-base Variables	Semirecumbent Mean ± S.E.	Semirecumbent Range	Supine Mean ± S.E.	Supine Range	Mean Difference (supine-semi-recumbent)	Significance (P value)
Preop						
$PaCO_2$ (mm Hg)	37.2 ± 0.4	34 – 41	36.7 ± 0.7	29 – 42	−0.5	N.S.*
Base excess (mEq/L)	1.8 ± 0.5	−3 to 8	1.6 ± 0.5	−3 to 7.5	−0.2	N.S.
Postop Day 1						
$PaCO_2$ (mm Hg)	39.1 ± 0.8	29 – 46	37.4 ± 0.7	29 – 45	−1.7	<0.01
Base excess (mEq/L)	1.0 ± 0.6	7 to −2.7	0.1 ± 0.6	4.9 to −4.8	−0.9	<0.01
Postop Day 2						
$PaCO_2$ (mm Hg)	40.0 ± 0.9	34 – 47	38.9 ± 0.9	30 – 46	−1.1	<0.01
Base excess (mEq/L)	2.9 ± 0.7	8.1 to −1.6	2.1 ± 0.7	7.5 to −5.2	−0.8	<0.01
Postop Day 3						
$PaCO_2$ (mm Hg)	40.5 ± 1.0	33 – 45	40.4 ± 1.1	31 – 46	−0.1	N.S.
Base excess (mEq/L)	3.9 ± 0.9	10.5 to, −2.3	3.7 ± 0.9	11.2 to −2.5	−0.2	N.S.

*N.S. = Not statistically significant using Student's *t*-test evenness of ventilation would tend to promote arterial hypoxemia. LeBlanc's study indicated that the age at which "closing volume" started to occur within the tidal range in non-obese subjects was about 65 years in the upright position and 44 years in the supine position. However, an extrapolation of these data to our markedly obese patients is not possible.

Alexander et al.[1] measured postoperative lung function to identify the mechanism of the observed hypoxemia. He demonstrated that all lung volumes were reduced following abdominal operations and the reductions were most severe after upper abdominal procedures. In his patients, there was a mean reduction of 28% in the FRC on postoperative day one. He also suggested that after surgery, the lung volume at which airways close [closing volume (CV)] might remain relatively unchanged while FRC decreased. Thus, there would be an increased likelihood of maldistribution of the tidal volume, mismatching of ventilation with perfusion, and thereby hypoxemia. Subsequently, Alexander et al.[2] were able to show a significant correlation between the (FRC-CV) relationship and arterial oxygenation.

Craig et al.[4] collected the only available data relating the effect of a change in posture on gas exchange. In 22 normal subjects the change in arterial oxygenation with change in position from seated to supine, as well as changes in the relationship of breathing level (FRC + tidal volume) to closing volume were evaluated. They postulated that alterations of gas exchange from the seated to the supine position would result from the interaction of three factors: 1) the increased cardiac output in the supine position,[9] with its effect on the mixed venous oxygen content;[11] 2) the increased uniformity of perfusion distributions and of regional ventilation/perfusion (V/Q) relationships in the supine lung;[5] amd 3) the increased involvement of the lung volume by "airway closure" in the supine position[7] tending to retard dependent zone ventilation and to lower dependent zone V/Q relationships. Arterial oxygenation would be improved by the first two factors, but impaired by the third. Craig found that the FRC decreased in the supine position, whereas "closing volume" was unchanged. The arterial oxygenation changes correlated directly with the degree of impingement of CV on the breathing level. However, when subjects were grouped specifically according to weight, age, or smoking history, no effect of posture on gas exchange was demonstrable.

In contrast to Craig's study in non-operated subjects, our resluts demonstrate that in markedly obese women, position has a significant effect on the Pa_{O_2} for 48 hours postoperatively. A likely pathophysiologic explanation for our findings is that in obese patients the additive effect of a reduced lung volume preoperatively, an abdominal vertical incision with its attendant pain and splinting, and the assumption of supine posture cause the increased involvement of the lung volume by "airway closure" during the first 48 hours after operation. As FRC returns toward preoperative levels by postoperative day three, the overall effect of position change on arterial oxygenation is no longer demonstrable.

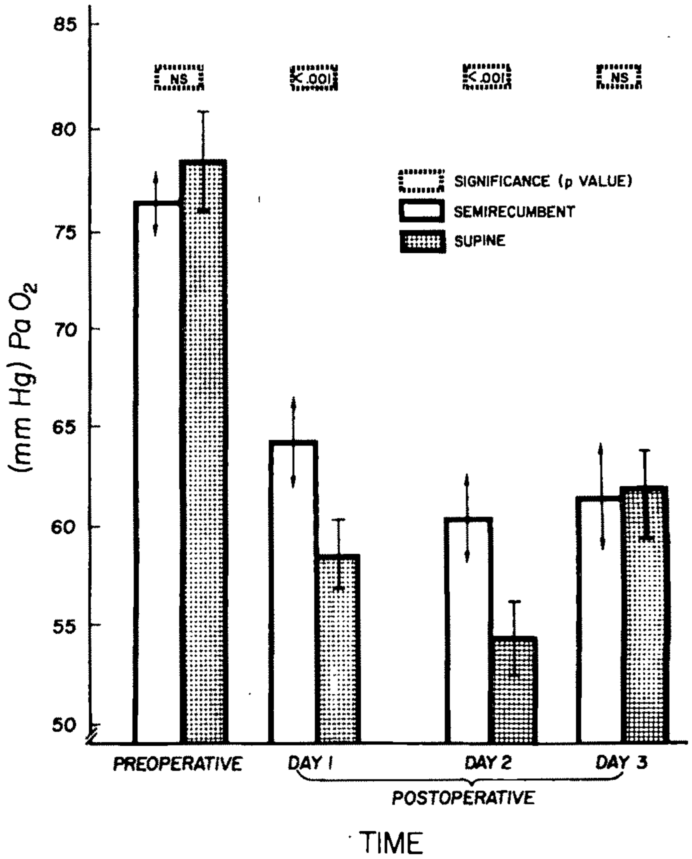

FIG. 1. Arterial oxygen tension (mean ± S.E.) in 22 obese female subjects in the semirecumbent compared to the supine position preoperatively and on each of postoperative days one through three. Preoperatively and on postoperative day three, no positional effect on Pa_{O_2} was demonstrable. On postoperative days one and two, however, a change to the supine position resulted in a statistically significant decrease ($P<0.001$) in Pa_{O_2}. Significance is considered as between the two positions not preoperative versus postoperative Pa_{O_2} values. NS = not statistically significant. All values were obtained with the patient breathing room air at rest.

In conclusion, the present study indicates that, in obese subjects, the assumption of the semirecumbent versus the supine posture during the early postoperative period is a valuable therapeutic tool to improve gas exchange. The clinical implications for those concerned with postoperative and other forms of intensive care are apparent. It should be noted that our data concerning arterial oxygenation were collected in a group of young, non-smoking, obese, but otherwise healthy women with no evidence of cardiorespiratory disease. In obese patients with cardiorespiratory disease positional change is likely to have an even more marked effect on oxygenation. It is often routine to place all individuals (obese or non-obese) with any degree of cardiovascular instability in a head down position. The advisability of this maneuver should be seriously questioned in obese subjects, unless adequate care is given to control the airway (intubation), assist ventilation, and supplement the inspired air with oxygen.

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Staging Laparotomy in the Treatment of Metastatic Melanoma of the Lower Extremities

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Twenty-six consecutive patients with melanoma of the lower extremities metastatic to the superficial inguinal lymph nodes were subjected to laparotomy. No patient had preoperative evidence of tumor dissemination past the superficial inguinal nodes. However three patients (12%) had metastases to the liver or para-aortic lymph nodes documented at laparotomy and were not subjected to iliac and obturator lymph node dissection. One of these patients had concomitant local recurrence of melanoma at the ankle. The other two patients had superficial inguinal lymph nodes at least 5 cm in diameter, although two other such patients with similar 5 cm lymph nodes did not have positive intra-abdominal findings.

The remaining 23 of the 26 patients underwent ipsilateral iliac and obturator lymph node dissection, which proved positive in 3/23 patients (13%). Of these 23 patients undergoing iliac and obturator node dissection, 18 had clinically positive (and microscopically positive) superficial inguinal nodes prior to their dissection, while the remaining 5 patients had clinically negative (but microscopically positive) superficial inguinal nodes. The three cases of positive dissected iliac and obturator nodes occurred among the 18 patients with clinically positive superficial inguinal nodes (17%). Among the 5 patients with clinically negative, microscopically positive superficial groin nodes, there was no detectable deep inguinal nodal spread (or hepatic or para-aortic involvement).

THE SURVIVAL of melanoma patients with Stage II disease (metastatic to regional lymph nodes, but not beyond) varies widely in different reported series, as does the survival of patients with Stage III disease (disseminated past the regional lymph nodes).[5–8,10,11,13,14,16] In Stage III, melanoma for example, the 5-year survival figures vary from 0 to 17%.[13,16] This wide disparity may be due to variations in the accuracy of staging of melanoma patients The same may be true of Stage II melanoma. The reported 5-year survival for State II melanoma patients with microscopically confirmed metastases in dissected regional nodes varies from 0 to 38%.[5,14]

Lymphadenectomy is usually advised in Stage II melanoma. If metastases are truly limited to the dissected regional nodes, then lymphadenectomy should be curative for most of these patients. However, if gross or microscopic metastases are growing outside the regional nodes, radical surgical attack on these nodes cannot be carried out with expectation of cure. If the superficial inguinal nodes are positive, deep inguinal node dissection has been advocated, but is controversial because of the poor prognosis in patients with deep inguinal involvement.[4]

The patient who seems to have Stage II melanoma of the lower extremities, but at laparotomy has occult liver metastases not apparent on liver scan or occult metastases to the para-aortic lymph nodes, has melanoma which is "Stage III-surgically staged" (III-SS) melanoma. The documentation of these metastases will make a difference in the patient's prognosis and in the choice and evaluation of his therapy. Placing him in Stage III-SS will change the survival figures of both the Stage II and Stage III categories.

The following study was undertaken to determine the frequency of Stage III-SS melanoma in patients with melanoma of the lower extremities metastatic to the superficial inguinal lymph nodes. In these patients, there was histologic or cytologic evidence of tumor in the superficial inguinal lymph nodes, with an otherwise negative evaluation. A common, external and internal iliac, and an obturator lymph node dissection was performed through an abdominal incision.[17] At the same time, the patient was staged by needle or wedge liver biopsies and biopsies of para-aortic lymph nodes. If, upon opening the abdomen,

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the liver or para-aortic lymph node areas showed evidence of tumor, the procedure was terminated, the lymph node dissection was not performed, and the patient was placed on an immunotherapy-chemotherapy protocol.

Another purpose of the study was to correlate the intra-abdominal findings with the findings in the superficial groin. Specifically, the variation in degree of superficial inguinal nodal involvement (microscopic involvement, clinically apparent involvement or massive involvement) was correlated with findings in the iliac and obturator nodes, liver and para-aortic nodes.

Finally, we attempted to determine what additional morbidity resulted from laparotomy, which gave better exposure of the higher iliac nodes and which allowed a shorter subinguinal incision to be made, since the latter incision was used only for superficial inguinal node dissection, and not retroperitoneal dissection.

Materials and Methods

Patients with lower extremity melanoma metastatic to the inguinal lymph nodes were evaluated by the following parameters: history, physical examination, routine hematological, serum and urine studies, chest roentgenogram and tomograms, gallium scan, liver scan, brain scan, bone scan, and evaluation of immune competence. The primary lesion, if still present, was treated by wide excision of skin and subcutaneous tissue 4 cm around the lesion, including deep fascia. Split thickness skin graft was required for closure in all cases. If the primary lesion had been previously treated in a less aggressive fashion during the preceding 6 months, the old operative site was re-excised and grafted. A superficial femoral lymphadenectomy was performed if the primary lesion was a nodular melanoma, or if it was invasive to level 3 or deeper by the criteria of Mihm and Clark,[9] or if clinically suspicious lymph nodes were palpable in the groin. This procedure was performed through an incision below and parallel to the inguinal ligament. If the superficial groin dissection specimen was negative for metastasis, the patient was not entered into the study, and received no further lymph node dissection since we are aware of only one case in which there was deep inguinal involvement without microscopically detectable superficial inguinal involvement.[4] The patient was entered into the study if the superficial groin lymph nodes contained tumor, either upon histologic examination of the superficial groin dissection specimen or upon cytological examination of material obtained by fine needle aspiration[2] of superficial groin nodes. All patients with melanoma metastatic to the superficial groin who had no other evidence of disease dissemination, underwent staging laparotomy and were prepared for concomitant iliac and obturator lymph node dissection. Preoperative roentgenographic, scan or other suggestion of disseminated disease was evaluated by biopsy and frozen section at the time of surgery. Patients with abnormal liver scans were excluded except for a patient whose liver abnormality proved to be benign cavernous hemangiomas. At laparotomy, through a midline incision, the liver was carefully palpated and "blind" biopsies were usually obtained if no gross lesions could be identified. Needle (Vim Silverman or Manghini) or wedge biopsy, was carried out depending on the surgeon's preference and the adequacy of surgical exposure. Para-aortic lymph nodes were sought for biopsy. If frozen section demonstrated that these biopsies were tumor-free, then lymphadenectomy was performed starting at the aortic bifurcation on the involved side. The common, external and internal iliac nodes and obturator nodes were removed on the involved side.

Results

Twenty-five consecutive patients with primary melanoma of the lower extremity, with pathologic evidence of tumor in their superficial inguinal lymph nodes but no other preoperative evidence of tumor dissemination, were entered into the study. One additional patient had documented melanoma in a superficial groin node, with no evidence of a primary lesion. Twenty-one of the 26 patients had clinically positive superficial inguinal nodes prior to their removal, and are classified in Table 1 as being clinical Stage II prior to positive superficial groin dissection. Five patients entered the study because unsuspected microscopic nodal involvement was discovered on examination of superficial inguinal lymph nodes removed prophylactically. These patients are designated in Table 1 as clinical Stage I prior to positive superficial groin dissection. The age, sex, site and level of invasion of primary, liver enzyme results, surgical findings and outcomes are also presented in Table 1. Outside slides of the primary lesions were reviewed to determine the deepest level of invasion apparent on the occasionally limited submitted material.[9] Each of the 19 primary melanomas that were levelled showed invasion to *at least* 3, 4, or 5 (papillary dermisreticular dermis junction, reticular dermis, or subcutaneous fat).

All 26 patients underwent laparotomy. One patient had undergone a previous laparotomy because of filling defects on liver scan which proved to be cavernous hemangiomas. The remaining patients all had normal liver scans. As shown in Table 1, 5 of the 26 patients (19%) had mild liver enzyme abnormalities. One of these later proved at laparotomy to have small liver metastases, the other 4 did not. As summarized in Table 2, 3 of 23 patients (13%) whose laparotomies were otherwise negative for disseminated disease, were found to have positive iliac nodes. Liver biopsies were negative in these 3 patients, each of whom had palpable 2 cm superficial inguinal lymph nodes. No patient with clinically negative superficial groin nodes had positive intra-abdominal find-

TABLE 1. *Patient Data*

Case #	Age, Sex	Site of primary and level of inv.	Clinical Stage Prior to Positive Superficial Groin Dissection	Liver Enzyme Abnormality	Laparotomy Findings	Outcome
1	31,F	Ankle, 4	II	—	Liver bx positive (+), procedure terminated	Alive 6 mo. later on chemotherapy
2	44,M	Thigh, *	II	↑SGPT	Para-aortic nodes (+), liver bx (−), procedure terminated	Alive 5 mo. later on chemotherapy
3	52,M	Calf, 4	II	↑Bilirubin ↑SGPT	Liver bx (+), procedure terminated	Bony & pulmonary mets. 6 mo. later on immuno-chemotherapy
4	10,M	Inguinal, 5	II	—	Deep groin (−)	Alive 19 mo. postop, NED
5	15, F	Calif, 4	II	—	Deep groin (−)	Alive 2 yr. postop NED
6	33,F	Thigh, 3	II	Slightly ↑Alk. phos.	Deep groin (−)	Death 4 mo. postop, met. melanoma
7	27,M	Calf, 4	II	—	Deep groin (−)	Death 2 yrs. postop, met. melanoma
8	10,M	Toe, 5	II	—	Deep groin (−), liver bx (−), scalene node (−), bone marrow (−)	Alive with groin recurrence 10 mo. postop
9	50, F	Thigh, *	I	—	Deep groin (−), liver bx (−)	Alive 20 mo. postop, NED
10	50, M	Flank, *	I	—	Deep groin (−), liver bx (−)	Death 16 mo. postop with brain mets and groin recurrence
11	57, M	Tibia, 5	II	—	Deep groin (−), liver bx (−), scalene node bx (−)	Alive 17 mo. postop, NED
12	37, F	Thigh, 4	II	↑Alk. phos.	Deep groin (−)	Alive 19 mo., NED
13	72, F	Calf, *	II	—	Liver bx (−), para-aortic nodes (−), deep groin (+), popliteal nodes (+)	Dead 19 mo. postop of met disease
14	71, M	Foot, *	II	—	Deep groin (+), liver bx (−)	Dead 13 mo. postop of metastatic disease with groin recurrence
15	42, F	Hip, 3	II	—	Deep groin (−), liver bx (−)	Alive 11 mo., NED
16	31, M	Calf, 4	I	—	Deep groin (−), liver bx (−)	Alive 10 mo., NED
17	43, F	Lower Leg, 3	II	—	Scalene nodes (−), deep groin (−)	Alive 6 mo., NED
18	30, M	Foot, 4	II	—	Deep groin (−), liver bx (−)	Alive with recurrence 3 mo. postop
19	74, F	Foot, *	II	—	Deep groin (−), liver bx (−), scalene nodes (−)	Alive 4 mo., NED, then died of CVA. No autopsy
20	51, F	Thigh, 3	II	↑Alk. phos. ↑Amylase	Deep groin (−)	Dead 22 mo. postop of met disease
21	14, F	Buttock, 3	II	—	Deep groin (−)	Metastases to lungs, bone and subcutaneous tissue 9 mo. postop
22	26, F	Thigh, 3	II	—	Liver bx (−), deep groin (−)	Alive 4 mo., NED
23	57, F	Thigh, *	II	—	Liver bx (−), deep groin (−)	Alive 2 mo., NED
24	54, F	Calf, 5	I	—	Deep groin (−)	Alive 2 mo., NED
25	41, F	Calf, 4	I	—	Deep groin (−)	Alive 1 mo., NED
26	34, F	* *	II	—	Liver bx (−), deep groin (−)	Alive 2 mo., NED

*Unknown

ings when laparotomy was performed because of microscopic discovery of superficial groin node positivity.

The only complication of laparotomy in these 26 patients was the development of postoperative intestinal obstruction in one patient requiring operative lysis of adhesions. There was one case of massive lymphedema of the operated extremity, and no major groin skin sloughs.

Two of the 26 patients in this series were found to have positive liver biopsies and one had a positive para-aortic

TABLE 2.

Clinical Stage Prior to Positive Superficial Groin Dissection	Incidence of Liver or Para-Aortic Node Positivity	Incidence of Positivity in Dissected Deep Groin Nodes*
I	0/5 (0 %)	0/5 (0 %)
II	3/21 (14%)	3/18 (17%)
TOTAL	3/26 (12%)	3/23 (13%)

*Does not include the three patients with liver or para-aortic node positivity since no deep groin dissection was performed in these patients.

lymph node biopsy. The surgical procedure was, therefore, terminated without therapeutic iliac or obturator lymph node dissection in these three patients (12% of the series) whose histories are summarized below:

Case Reports

L.F., a 31-year-old blonde, fair-skinned woman, underwent removal of a nodular melanoma invasive to level 4 from the left ankle 1½ years prior to admission. Melanoma recurred locally in the skin graft site one month prior to admission. At that time, a superficial inguinal node dissection yielded 5 positive lymph nodes, and she was transferred to NCI. A seroma at the superficial groin operative site was negative for tumor cells on cytologic examination. A bone scan showed slightly increased uptake in her left pelvis where no x-ray abnormalities were apparent. Gallium scan showed increased uptake in the ipsilateral popliteal area although no palpable nodes were present. The remainder of her evaluation, including liver scan and liver function tests were all within normal limits. If no liver or para-aortic disease had been discovered at surgery, the planned procedure would have included iliac and obturator node dissection, popliteal exploration and possible node dissection, and wide re-excision of recurrent disease in the old skin graft near the left lateral malleolus, with removal of the underlying tendons at the base of the previous skin graft. However, although the liver appeared normal at laparotomy, careful palpation suggested the presence of several 2 cm masses 1-2 cm below the capsular surface. Two needle biopsies and, finally, wedge excision biopsy confirmed these were metastatic melanoma. Therefore, the procedure was terminated without deep inguinal dissection or re-excision of the local recurrence in the leg. The patient was placed on an immunotherapy-chemotherapy treatment protocol and has done well for 6 months.

R.A., a 52-year-old Caucasian man was seen at the NIH 15 months after excision of a level 4 nodular melanoma on his calf. This "mole" which had been present all his life had started to enlarge after accidental trauma. Eight months after primary excision, the lesion recurred locally with multiple satellite nodules. When admitted to NIH he also had three grossly enlarged (2-7 cm) lymph nodes palpable in the left inguinal area. The only other abnormalities were a mildly increased total bilirubin (1.4 mg/100 ml) and SGPT (84 U/L vs normal 2-45). Liver scan was normal, and the enzyme elevations were attributed to alcohol ingestion. At laparotomy, several punctate lesions visible on liver surface were positive on biopsy. Accordingly, lymph node dissection was not carried out. The patient received immunotherapy and later chemotherapy but deteriorated over the next 5 months with pulmonary and osseous metastases. The leg recurrence and large superficial groin metastases presented no significant local problems during the remainder of the patient's life.

W.G., a 44-year-old Caucasian man, had a mole on this right medial thigh his entire life. After the patient noted a mass in his groin, the mole was biopsied and found to be malignant melanoma. Lymphangiogram was negative. On referral to NCI, the patient had three discrete groin masses, 5-12 cm in diameter, and a questionably palpable external iliac pelvic mass on the same side. The only other abnormality was mildly elevated SGPT. At laparotomy, enlarged firm lymph nodes were adherent to the external iliac artery. Liver biopsy was negative, but frozen section examination of a small para-aortic lymph node was positive despite the previously negative lymphangiogram. The procedure was terminated. The patient was placed on chemotherapy to which the groin masses responded although metastatic disease later progressed.

Discussion

On preoperative physical examination the three patients whose subsequent laparotomy showed tumor in the liver or para-aortic nodes had either large tumor masses in the superficial groin (two cases), or local recurrence at the primary grafted site (one case). Patients with only microscopic superficial inguinal node involvement or clinically positive superficial inguinal lymph nodes 2 cm or less in diameter, exhibited no tumor within the abdomen, except for involvement of the iliac lymph nodes in 3 patients, each of whom had clinically positive superficial inguinal nodes. It is of interest that the two patients with positive liver biopsies had normal liver scans. The positive para-aortic node involvement in a third patient was found only on microscopic evaluation of a small hard lymph node following negative lymphangiography.

Thus, in melanoma as in carcinoma of the cervix,[12] Hodgkin's disease,[3] and other cancers, surgical staging shows that more patients have disseminated disease than can be detected by routine preoperative evaluation. We feel that patients found to have visceral or para-aortic nodal melanoma should not be subjected to deep inguinal lymphadenectomy. In view of the morbidity associated with such surgery, these patients, in our opinion, should be classified as "minimal" Stage III disease and become candidates for chemotherapy, or immunotherapy. Since these patients carry a minimal tumor burden compared to most Stage III patients, they *may* have an increased chance of responding to adjunctive therapy, although this is unproven. Accurate staging of patients and removal from Stage II classification of patients with occult disseminated disease will allow the effectiveness of surgical procedures such as lymphadenectomy and adjunctive therapy, in Stage II patients to be properly evaluated. The removal of minimal Stage III patients from Stage II categories will result in an apparent increased effectiveness of any treatment for Stage II patients.

The disease in the liver in the two patients with liver involvement was detected only after careful palpation and wedge biopsies of selected areas. Neither of these patients had gross involvement likely to be detected by blind needle biopsy. The external surface of the liver was normal in one of these two patients with positive liver biopsies, and therefore, peritoneoscopy would have failed to detect involvement, although Sauer has shown that peritoneoscopy could be substituted for laparotomy in some patients.[15]

The question arises as to whether it is useful to surgically "debulk" large tumor masses in the superficial groin even when hepatic metastases are present. Our experience with these three patients as well as other Stage III patients with bulky nodal disease suggests that the melanoma patient with liver involvement is rapidly confronted with serious complications of disseminated tumor which produce clinical problems more severe than those due to the enlarged groin nodes.

A related question is whether removal of extrahepatic disease may facilitate the rate of spontaneous regression of melanoma metastatic to the liver. We have not observed regression of visceral metastases after debulking of extra-visceral disease. To the contrary, no debulking was done in the only patient in our experience who underwent documented regression of visceral metastases.[1] This 58-year-old woman had metastatic melanoma of the leg with satellitosis and liver metastases histologically documented 13 years ago. She underwent spontaneous regression of the hepatic metastases documented at a second laparotomy (for hysterectomy) 6 years later. This patient is without evidence of disease an additional 7 years later, although there was no attempt to debulk the extrahepatic disease. To our knowledge there is no evidence that spontaneous regression of visceral disease would be more frequent if other disease is debulked.

The question may be raised as to whether patients exhibiting gross superficial inguinal involvement with melanoma should be considered categorically inoperable. We feel that bulky superficial nodal disease should not, in and of itself, exclude a patient from an attempt at surgical extirpation. For example, patients #19 and #20 in Table 1 had 5 cm masses in the superficial groin, resected together with other negative superficial and deep lymph nodes. Although such patients usually succumb to metastatic disease, some do not.

Hopefully, in the future, accurate, noninvasive techniques will become available and facilitate staging of melanoma patients. In the meantime, we recommend that melanoma patients with bulky inguinal-femoral lymph node involvement be considered for a staging laparotomy of the type that we have described. Those patients with positive liver or para-aortic node biopsies should be treated systemically rather than surgically in our opinion, until more evidence is presented regarding the value of debulking procedures which may be especially morbid in these patients whose bulky nodal disease may be adherent to iliac or femoral vessels, or skin overlying the femoral triangle.

Patients with clinically positive (but not massive) superficial inguinal nodal involvement had no liver or para-aortic spread documented at staging laparotomy, but had a positive transabdominal deep inguinal dissection in 13% of the cases. We are continuing to evaluate the staging laparotomy approach in these patients.

Finally, patients with only microscopic superficial inguinal involvement have had no liver, para-aortic or deep inguinal involvement in this small series. Should this observation remain accurate, a superficial inguinal dissection may be adequate surgery in patients with clinically negative but microscopically positive superficial inguinal lymph nodes.

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Adenocarcinoma of the Pancreas:

A Statistical Analysis of Biliary Bypass vs Whipple Resection in Good Risk Patients

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A series of 297 patients with adenocarcinoma of the head of the pancreas was reviewed. Forty-eight patients were identified with disease limited to the pancreas or adjacent tissues. Twenty-four patients underwent Whipple resection. A second group of 24 patients underwent elective biliary bypass. No patient had liver, omental or peritoneal metastases. All cases of ampullary carcinoma and islet cell tumors were excluded. Assessment of clinical and laboratory parameters revealed the two groups to be statistically comparable. There were no 5-year survivors in either group. Mean duration of survival was not significantly different. Life table analysis showed no significant difference between the survival rates of the two groups. Frequency of clinic followup, rehospitalization and reexploration were used to assess palliation. Success of palliation was poor in both groups and no statistically significant differences were noted. Surgical mortality in the resected group was 8% and did not differ from the 4% surgical mortality in the bypass group. Surgical morbidity was significantly higher in the resected group. Implications of this data in the management of patients with resectable carcinoma of the pancreas are discussed.

FOUR DECADES after its introduction, the precise role of pancreaticoduodenectomy in the overall management of patients with adenocarcinoma of the pancreas remains to be defined. Cure of this malignancy, in the individual patient, is only possible by pancreatic resection. However, an average operative mortality rate of 20% and an overall 5-year survival of less than 5% nationally[20] have convinced occasional surgeons of broad experience to abandon resection.[6,10] This position assumes that adenocarcinoma of ductular origin is virtually incurable with the traditional pancreaticoduodenectomy and that the degree of palliation and duration of life are as high with biliary bypass as with resection of the primary pancreatic tumor.[6]

The available literature provides little reliable data either to support or refute this thesis. Large variation in surgical mortality and unspecified criteria of selection make evaluation and comparison of survival and cure rates difficult. There have been few attempts in the past to confine surgical reports specifically to adenocarcinoma of ductular origin. Frequently ampullary carcinoma, common duct carcinoma, islet cell tumors and duodenal carcinoma are included in the 5-year survival statistics for pancreaticoduodenectomy.[15]

In assessing the end results of Whipple resection, the patients subjected to pancreaticoduodenectomy for cure are frequently compared to the larger group of unsalvagable patients undergoing biliary bypass for palliation. Not surprisingly, the group suitable for resection lives longer, enjoys better palliation and provides the only documented 5-year survivors. Meaningful evaluation of the end results of cancer therapy, requires that both the cell type and the clinical stage of the tumor at the time of initial therapy be comparable. Clearly, if the true role of pancreatic resection in adenocarcinoma of the pancreas is to be established, the above principles must be respected.

To rigorously document the alleged equivalence of biliary bypass to resection would require a prospective trial in which jaundiced patients with adenocarcinoma suitable for resection were randomly assigned to bypass or Whipple resection. Obviously, this ideal can not be realized at this time because a majority of physicians and surgeons would consider such randomization unethical.

A first approximation to such a study can be achieved,

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TABLE 1. Parameters in patient's history and physical findings used to assess comparability of groups. Mean ± 1 S.E.M.

	Whipple Resection	Biliary Bypass	P Value
Duration Symptoms (Mo.)	3.3 ± 0.8	3.2 ± 0.4	.88 (NS)
Weight Loss (Lbs.)	16.9 ± 3.5	17.9 ± 3.4	.19 (NS)
Duration Jaundice (Wks.)	2.5 ± 0.3	2.5 ± 0.4	NS
Hepatomegaly (%)	14/19	15/23	.39 (NS)
Palpable G.B. (%)	7/23	8/24	.76 (NS)
% No Jaundice	15%	12.5%	.67 (NS)
Age	60.1 ± 1.7	65.4 ± 1.6	.025
Sex M/F (%)	10/14	13/11	NS

however, by retrospective analysis. The major deterent to such a review in the past has been the reservation of bypass surgery for those patients with disseminated disease or medical contraindications to resection. Only if retrospective review produces a group of patients with localized disease subject to biliary bypass can a legitimate comparison to patients resected for cure be made.

This study was undertaken to identify two such groups of patients, assess their comparability and statistically compare surgical mortality, mean survival time and success of palliation.

Methods

All medical records at the Rush-Presbyterian-St. Luke's Medical Center coded *Carcinoma of the Pancreas or Whipple Resection* from July 1, 1966 to June 30, 1974 were reviewed. A total of 297 patients were available for review.

TABLE 2. Laboratory data employed to assess comparability of groups. Mean ± 1 S.E.M.

	Whipple Resection	Biliary Bypass	F Value
Hemoglobin (Gms.)	12.8 ± 0.4	13.2 ± 0.3	.74 (NS)
Prothrombin Time (%)	69.2 ± 5.0	71.2 ± 4.9	.29 (NS)
Albumin (Gms.)	3.7 ± 0.3	3.9 ± 0.2	.59 (NS)
SGOT (Units)	185 ± 29	161 ± 25	.63 (NS)
Alkaline Phosphatase	15.8 ± 2.4	16.3 ± 1.8	.14 (NS)
Total Bilirubin	11.5 ± 1.7	11.0 ± 1.5	.72 (NS)
Fasting Sugar	146 ± 7.5	133 ± 12.8	.20 (NS)

Of these, 135 patients were initially excluded because no exploration was performed. In general these patients had advanced disease or had been treated initially elsewhere and were admitted for chemotherapy or terminal care.

One-hundred-sixty-two (55%) patients underwent exploratory laparotomy. Of these, 114 were found to have disseminated disease. Most underwent biliary bypass but will not be considered further in this report.

The remaining 48 patients consisted of 24 patients subjected to pancreaticoduodenectomy for cure of adenocarcinoma of the head of the pancreas and a second group of 24 patients with malignant disease limited to the pancreas or adjacent tissues which underwent elective biliary bypass. None of these cases had liver, peritoneal or omental metastases. Only cases of ductular adenocarcinoma arising in the head of the pancreas were considered. All cases of ampullary carcinoma, common duct carcinoma, islet cell tumors, cystadenocarcinoma, duodenal carcinoma and leiomyosarcoma of the duodenum were excluded.

Of the 24 patients bypassed, 12 had regional extension of the tumor involving adjacent vital vascular structures which precluded resection. The remaining 12 patients had strictly local disease confined to the pancreas which might have been resected. These 12 patients were either elderly or, more commonly, were in the care of several surgeons who had abandoned the Whipple procedure in the belief that the end results did not justify its use. Figure 1 summarizes in graphic form the overall disposition of this series of 297 patients.

The medical records of these 48 patients with disease grossly confined to the pancreatic head were reviewed and factors indicative of the clinical stage of their disease were tabulated. Review of the operative records and pathology reports provided a reasonably accurate description of the gross pathology and clinical stage of the tumor (local, regional or disseminated). These combined data were used to determine the clinical comparability of the two groups.

Each patient was followed until death or date of latest clinic followup. Surgical mortality, morbidity, duration of survival and success of palliation were recorded. Only one patient in the combined series of 48 patients was lost to followup. Success of palliation was estimated by the frequency of clinic visits, frequency of rehospitalization and frequency of additional surgical procedures.

Pathology review confirmed the tissue diagnosis of adenocarcinoma of the pancreas in all resected patients. Tissue was unavailable in 66% of the patients subjected to biliary bypass. Lacking liver and nodal metastases, these patients would have required pancreatic biopsy to confirm the clinical suspicion of malignant obstruction. This was not felt to be indicated by the operating surgeon. The typical gross pathology of pancreatic cancer, as described by Warren,[22] was identified in each case. In addition, operative cholangiography and cholecystectomy excluded biliary calculi and documented complete common duct obstruction in many cases. Roux–Y choledochojejunostomy or Roux–Y cholecystojejunostomy were the preferred means of bypass during this period (19 cases). Four patients had loop cholecystojejunostomy and one patient underwent choledochoduodenostomy. Fourteen patients underwent gastrojejunostomy electively at the initial procedure.

Comparability of the treatment group parameters was determined by use of the unpaired *t* test. Chi square analysis was used for enumeration data. Differences in mean survival times were evaluated by *t* test and 95% confidence limits for population means. Life table analysis was used to compensate for those patients still living but having only short term followup. Differences in life table cumulative survival rates were compared by Chi square analysis as described by Spratt and Donegan.[21]

Results

There was no significant difference in the sex or duration of symptoms of the patient in the two groups. Similarly, the magnitude of weight loss, duration of jaundice and percentage of patients presenting without jaundice were similar (Table 1). Physical findings of hepatomegaly and presence of a palpable gallbladder were approximately equal in both groups. As might be expected, the patients selected for resection were significantly younger (P=0.025) than the group undergoing biliary bypass.

Inspection of Table 2 reveals no difference in the level of hyperglycemia, anemia or abnormal liver function test between the two groups. Elevation of serum bilirubin, transaminase, albumin and prothrombin time were virtually the same. These data would suggest common duct obstruction of approximately equal duration.

Table 3 records the surgical mortality in the group of resected and bypassed patients. One of 24 patients (4%) subjected to bypass died in the postoperative period of respiratory insufficiency secondary to aspiration pneumonia. Of the 24 patients subjected to pancreaticoduodenectomy, none died within 30 days. The two hospital deaths (8%) occurred at 65 and 69 days. Although beyond the traditional 30 day surgical period, both deaths related directly to the surgical procedure and are appropriately listed as surgical mortality.

The remaining data in Table 3 confirm what would be intuitively expected. The patients subjected to resection required significantly longer recovery periods, longer surgery, more transfusions and suffered substantially increased rate of surgical morbidity related directly to the surgical procedure. In contrast to these morbidity rates, the mortality rates are insignificantly different and support the comparability and general good risk of both groups.

TABLE 3. Indices of magnitude of therapy.

	Whipple Resection	Biliary Bypass	P Value
Duration medical (pre-op) hospitalization (days)	10.3 ± 0.9	9.8 ± 1.3	.75 (NS)
Duration surgical (post-op) hospitalization (days)	31.3 ± 3.9	15.6 ± 1.2	.001
Duration surgery (hrs)	8.4 ± 0.4	4.0 ±0.4	.001
Transfusion (units)	5.4 ± 0.7	0.5 ± 0.3	.001
Surgical morbidity	12/24 (50%)	3/24 (12.5%)	.02
Surgical mortality	2/24 (8%)	1/24 (4%)	NS

Mean ± 1 S.E.M.

Mean duration of survival of the two groups is recorded in Table 4. These survival figures exclude operative deaths and those patients still living as of December 31, 1974. There is one survivor and one patient lost to followup at 3 months in the bypass group. Five patients are still living in the resection group, the longest being 21 months postoperative. There are no 5-year survivors in either group. The single survivor in the bypass group is alive and apparently well 24 months postoperative. Of the 5 surviving patients in the group undergoing Whipple resection, three are alive and well at 21, 10 and 12 months. Two are alive with documented residual disease at 10 and 22 months. In order to compensate for these patients in evaluating survival rates, life table analysis will be used. Inspection of Table 4 reveals no significant difference between mean duration of survival or the 95% confidence limits for population means. This holds whether the resected group is compared to the total group of bypassed patients or to the smaller but more favorable

TABLE 4. Mean survival (months) ± 1 S.E.M. and 95% confidence units for population means.

	Whipple Resection (n=17)	Biliary Bypass (n=21)	P Value
Mean Duration Survival (Mo.)	10.6 ± 1.4	8.1 ± 1.0	.33 (NS)
95% C.L. (Mo.)	7.7 - 13.6	6.0 - 10.2	
	Whipple Resection (n=17)	Local Disease Bypass (n=10)	
Mean Duration Survival (Mo.)	10.6 ± 1.4	8.6 ± 1.3	.33 (NS)
95% C.L. (Mo.)	7.7 - 13.6	5.7 - 11.4	
	Regional Disease bypass (n=11)	Local Disease Bypass (n=10)	
Mean Duration Survival (Mo.)	7.7 ± 1.6	8.6 ± 1.3	.68 (NS)
95% C.L. (Mo.)	4.8 - 10.6	5.7 - 11.4	

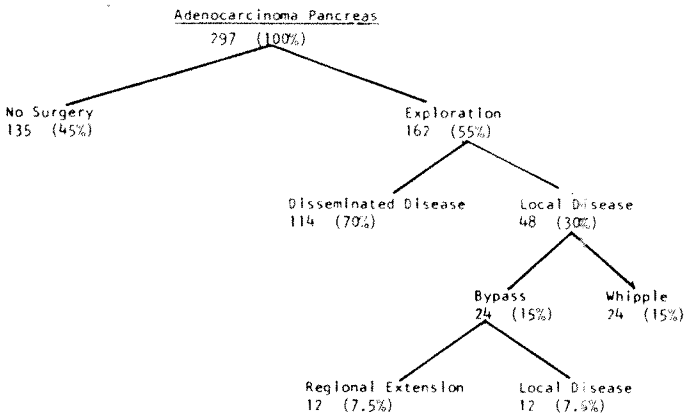

FIG. 1. Tabular List of 297 Patients by Stage of Tumor.

group which might have been resected but was not. In addition, comparison of the two subgroups of patients undergoing bypass reveals no significant difference in their duration of survival.

Table 5 and Figure 2 record the life table analysis of cumulative survival for the three groups under consideration. Chi square analysis of the % cumulative survival of the resected group compared to both the total bypass group and the smaller bypass group with local disease reveals no significant differences.[21]

TABLE 5. Life Table % Cumulative Survival.

	A	B	C
Interval (Mo.)	Whipple Resection (n=22)	Total Bypass (n=21)	Local Bypass (n=12)
2	1.00	.957	1.00
4	.955	.778	.827
6	.821	.734	.827
8	.689	.504	.643
10	.648	.367	.460
12	.505	.229	.276
14	.394	.184	.276
16	.330	.092	.091
18	.330	.092	.091
20	.198	.092	.091
22	.198	.046	.091
24	.198	.046	.091
26	.000	.046	.091
28	.000	.046	.091

$\chi^2 = 11.06$ (A vs. B)
D.F. = 13
p = .524

Table 6 represents an attempt to evaluate the success of palliation in these two groups of patients. This is a notoriously difficult factor to evaluate. Not only are symptoms frequently subjective but office and clinic records are often too inaccurate for proper evaluation. Since jaundice is uniformly relieved by either procedure, it cannot be employed to judge surgical success. No patient in either group had recurrence of jaundice because of failure of the extrahepatic bypass.

The principal problems of palliation relate to progressive pain, weight loss, anorexia, malabsorption and diarrhea. One would hope that removal of the primary tumor would ameliorate these symptoms more successfully than bypass. Unfortunately, in this series, this did not prove to be the case. Only one patient subjected to resection has gained weight and returned to work. She is now alive and well, 21 months following surgery.

The number of rehospitalizations and subsequent reexplorations can serve, at least indirectly, as an index of progressive symptoms. Examination of Table 6 reveals no significant differences between the two groups. The resected group required additional hospitalization and surgery as frequently as the group subjected to biliary bypass. No "second look" explorations were done in either group. All patients were reexplored for complications of the tumor or their original surgery.

It is possible that a number of the patients undergoing biliary bypass did not have adenocarcinoma of the head of the pancreas since only 8 of the 24 patients had a positive biopsy. As noted above, both the clinical history and gross surgical pathology were consistent with pancreatic carcinoma. As Table 7 indicates, when the mean duration of survival is compared for those patients with positive biopsies and the larger group lacking such histologic confirmation of pancreatic cancer, no significant difference in survival is noted. Had the latter group contained patients with benign disease, this outcome would seem unlikely. Finally, the mean survival of 7.4 months in the group lacking tissue diagnosis is more consistent with pancreatic carcinoma than other alternatives which might have been included such as islet cell tumor or chronic pancreatitis.

Discussion

Caution must be exercised in extrapolation of these data to the general population of patients with malignant obstruction of the common duct. It must be stressed that these two groups consisted entirely of elderly patients with adenocarcinoma of ductular origin arising in the head of the pancreas. The less common periampullary lesions having a more favorable prognosis has been explicitly excluded.[15,16,22,23] Consequently, these figures should not be applied prospectively unless the cell type is known. Resection for such periampullary lesions remains appropriate.

In addition, it must be stressed that all these patients had clinical histories of several months duration, progressive obstructive jaundice, marked weight loss and a large pancreatic mass at surgery. While they are typical of patients with carcinoma of the pancreas, occasionally a middle-aged (45-60 years) patient presents with recent jaundice and minimal weight loss. At surgery, a small mass is found. The data reported here should not be interpreted to indicate that such unusual patients will necessarily do as well with bypass. They may do so but the end results reported here strictly apply only to the more typical patient with ductular adenocarcinoma of the head of the pancreas. Whether biliary bypass can produce equivalent results in such an unusual group can not be inferred from our data.

Such unusual patients should be subjected to resection in our opinion only if a knowledgable surgeon is convinced cure is possible, if the procedure can be performed with a mortality less than 10% and if no obvious metastatic adenopathy is identified.[9] With these stipulations, these unusual patients certainly will do no worse than if bypassed and will have been provided with their only possible chance for cure.

When faced with the more typical elderly patient, our data strongly suggest that, statistically, they will do as well with biliary bypass as with resection of the pancreatic tumor. This holds true whether the end point is mean duration of survival or success of palliation. There were no 5-year survivors from Whipple resection in this series.

Table 8 lists 16 series in the past 12 years in which 5-year survivors for carcinoma of the head of the pancreas have been claimed. A total of 20 survivors in a combined series of 497 patients yields a survival rate of 4%. The mean duration of survival is 13.9 months with a surgical mortality of 21%. The end results of resection in our series are notably poorer than several individual reports in Table 8. There is however, no difference in overall mean survival times at the 5% level ($P=0.09$) when the collected series is compared to the current series of 24 Whipple resections.

Although it is conceivable that unknown factors produced a poor risk population, our surgical mortality of 8% argues against this interpretation. In addition, pathology reports on the resected specimens revealed surgical margins to be free of microscopic disease in 13 of the 14 patients for which information was available. Six of the 14 patients had metastatic disease in peripancreatic nodes. The majority of these procedures were performed by senior surgical staff with long interest in pancreatic surgery. Review of operative records revealed the techniques of resection conformed to generally accepted surgical principles. It seems more likely, therefore, that the lower mean duration of survival noted here reflects the exclusion of relatively good risk periampullary tumors and that the mean survival of 10.6 months is a reasonable estimate for ductular adenocarcinoma arising in the head of the gland.[2,6,9,12,23]

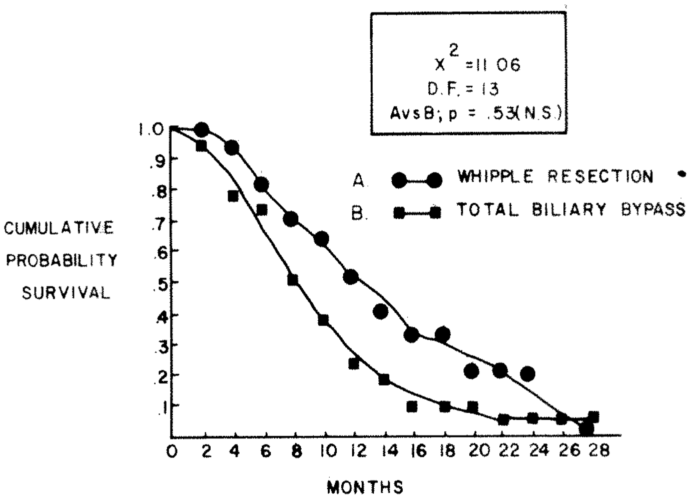

FIG. 2. Life Table Survival Rate: Whipple vs. Bypass.

Review of the recent literature reveals 6 retrospective reports which compare the results of Whipple resection to the results of bypass in good risk patients with local disease. Feduska et al.[7] found 60% successful palliation with resection and 53% with bypass. Crile[6] found comparable survival in 10 resected patients and 28 good risk patients subjected to biliary bypass between 1953 and 1966. Monge[13] compared 23 patients subjected to bypass in Duluth, Minnesota to a previous series of resections at the Mayo Clinic. The bypassed patients lived 12 months. Although identical to the mean survival for adenocarcinoma of the pancreas at the Mayo Clinic, the patients were not strictly comparable since the previous series of resections at the Mayo Clinic included islet cell tumors and cases of cyst adenocarcinoma.

Lund[12] compared 24 Whipple resections with 59 patients bypassed in Copenhagen and found no significant difference in mean survival. Recently, Hertzberg[9] reported 12 patients with carcinoma of the head of the pancreas with similar group of highly selected good risk

TABLE 6. Frequency of hospitalization and subsequent surgery in patients surviving initial surgery. $X^2=.32$. $P=0.95$.

	Number	Whipple Resection (n=22)	(n=23) Biliary Bypass
Subsequent hospitalization	0	26% (6/22)	34% (8/23)
(Palliation index)	1	52% (11/22)	56% (13/23)
	2	13% (3/22)	4% (1/23)
	3	9% (2/22)	5% (1/23)
Subsequent surgery	0	64% (14/22)	78% (18/23)
	1	27% (6/22)	22% (5/23)
	2	9% (2/22)	0%

$\chi^2 = .32$
$P = 0.95$

TABLE 7. Comparison of Survival: Bypass patients with and without tissue diagnosis. Mean Survival (months) ± 1 S.E.M. 95% confidence limits for population means.

	Biliary Bypass		
	Positive Biopsy (n=8)	No Tissue Biopsy (n=12)	P Value
Mean Survival (months)	6.4 ± 1.10	7.4 ± 1.0	.52 (NS)
95% C. L. (months)	3.8 - 9.1	5.1 - 9.7	

P = .5158

patients who were subjected to biliary bypass. The bypassed patients lived longer and there were no 5-year survivors in either group. Hermreck et al.[9] recently reported on the importance of pathologic staging in the surgical management of pancreatic carcinoma. When comparing the mean survival times for patients with Stage II and Stage III disease, no difference of significance was noted between resected and bypassed patients.

There is, therefore, considerable suggestive evidence to support the concept that, when compared to a matched population of patients with disease limited to the pancreas, the group of patients subjected to resection do no better than a similar group subjected to biliary bypass. Because of the substantial operative mortality (20%), the dismal salvage rate of 4% is not sufficient to provide an overall statistical advantage for Whipple resection.

It is true, of course, that resection remains the only therapy capable of curing the individual patient. Had all the patients in Table 8 been bypassed, 20 patients would have been denied the cure they apparently obtained.

In assessing the significance of this achievement, it should also be noted that 103 of these 496 patients died as a direct result of their Whipple resection and were therefore denied 10 to 14 months of additional life. It is the relative balance of this surgical mortality rate contrasted to a 4%, 5-year survival which the experienced surgeon must weigh in making a therapeutic judgement to resect.

Reducing the surgical mortality would, of course, simplify the decision considerably. It seems unlikely however that the mortality of resection can be substantially improved nationally even though occasional surgeons perform this procedure with a 5-10% mortality.

Despite a surgical mortality of 8% in this series, we have been unable to document better palliation or in-

Author	Institution	Number Patients	Number 5 Year Survivors	Operative Mortality %	Mean Duration of Survival (months)
Lansing 1972	Ochsner Clinic	22	1	27	---
Wilson 1974	Univ. Chicago	13	0	23	10.3
Morris 1966	Mass. General Hospital	26	2	42	---
Feduska 1971	Univ. Michigan	16	0	44	16.6
Buckwalter 1964	Univ. Iowa	28	0	23	13.6
Neilson 1967	Cooperative Study	16	2	18.6	15.0
Richards 1973	Univ. Minnesota	27	0	15	16.1
Hertzberg 1974	Sweden	12	0	8	17.0
Warren 1962	Lahey Clinic	89	1	12.4	---
Beall 1970	Univ. Missouri	6	0	16.7	11.3
Ashton 1973	UCLA	39	1	10.3	15.4
Glenn 1964	Cornell	25	1	24	---
Monge 1964	Mayo Clinic	107	8	21	12.0
Pope 1971	Univ. Texas	10	0	20	21.0
Crile 1970	Cleveland Clinic	10	0	10	8.5
Lund 1968	Copenhagen, Denmark	14	0	21	---
Hemrick 1973	Univ. Kansas	36	4	28	10.2
	TOTAL	496	20 (4%)		
	MEAN			21%	13.9 ± 1.0
	95% C.L.				11.6 - 16.2

TABLE 8. Mean Survival (months): Collected Series vs. Current Series P=0.09 (NS) Reported Series 1962-1974: Whipple Resection for Adenocarcinoma Head of Pancreas.[1,2,4,6-12,15-19,22]

crease survival with pancreatic resection. Our data support the hypothesis that in adenocarcinoma of the head of the pancreas, end results with biliary bypass in good risk patients are statistically equivalent to the results achieved with Whipple resection.

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Is Modified Radical Mastectomy Adequate for Axillary Lymph Node Dissection?

T. NEMOTO, THOMAS L. DAO

The effectiveness of axillary dissection by modified radical mastectomy was assessed by a comparison of the total axillary nodes removed by this operation to that by radical mastectomy. In a series of 121 consecutive radical mastectomies performed during the period of 1964 to 1969, we found that the number of axillary nodes removed ranged from 3 to 63 with a median of 22 and a mean of 23.4 per patient. In a subsequent series of 111 consecutive modified radical mastectomies performed between 1969 and 1973, the total axillary nodes removed ranged from 6 to 77 with a median of 24 and mean of 25.7 nodes in each mastectomy specimen. These results strongly suggest that axillary dissection in modified radical mastectomy is as complete as that in the Halsted radical mastectomy.

From the Department of Breast Surgery and Breast Cancer Research Unit, Roswell Park Memorial Institute, Buffalo, New York

TRADITIONALLY, surgical treatment of breast cancer combines local extirpation of the tumor with the removal of the regional lymph nodes *en bloc*. Any less procedure than this radical approach has often been considered as inadequate for curative treatment. In recent years, modified radical mastectomy has been employed by many surgeons$^{2-4}$ as a preferable method of treatment for breast cancer, but opponents say that this procedure cannot effectively remove all the axillary lymph nodes because of the preservation of the pectoral muscles. In a recent report, Hultborn et al.[1] claimed that from 1-10 additional nodes were left behind by modified radical mastectomy. In that study, a modified radical mastectomy was first performed by one surgeon, and this was followed by a radical mastectomy performed by another surgeon to remove the pectoral muscles and any lymph nodes that were not removed. These authors therefore concluded that a complete axillary dissection was impossible to achieve by modified radical mastectomy.

In this paper, we report that modified radical mastectomy is as efficient as the conventional radical mastectomy so far as the completeness of the dissection of the axillary lymph nodes is concerned.

Material and Method

Modified radical mastectomy has been employed as a standard curative operative procedure for women with breast cancer since 1969, by the Breast Department of Roswell Park Memorial Institute. A total of 109 women underwent modified radical mastectomies between 1969 and 1973 and they are the subject of this analysis.

A total of 121 radical mastectomies performed in the same department between 1964 and 1969 will serve as the standard for the comparison.

In the modified operation, the entire mammary gland is removed with pectoral fascia. Between the two pectoral muscles, the interpectoral fat pad is dissected from neurovascular supply to the pectoralis major. This fat pad containing lymph nodes is submitted separately for the pathological study. On entering the axilla, the pectoralis minor is transsected from the coracoid process to facilitate the exposure of the axilla. A complete axillary dissection is carried out up to the highest point.

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TABLE 1. *Comparison of Total Axillary Nodes Recovered*

	Radical Mastectomy	Modified Radical Mastectomy
Number of Patients	121	109
Number of Mastectomies	121	111
Axillary Nodes per Patient		
Median	22	24
Mean	23.4	25.7
Range	3-63	6-77

TABLE 2. *Recurrence Free Survival*

	Radical Mastectomy		Modified Radical Mastectomy	
Year	Negative nodes	Positive nodes	Negative nodes	Positive nodes
1	50/53(.94)*	52/68(.76)	42/45(.93)	49/64(.77)
2	48/53(.91)	39/68(.57)	31/33(.93)	38/54(.70)
3	45/53(.85)	31/68(.46)	24/26(.92)	23/41(.56)
4	45/53(.85)	27/68(.40)	16/19(.84)	19/33(.58)
5	44/53(.83)	26/68(.38)	7/10(.70)	13/24(.54)

*Recurrence free survivors/total (%).

The removed axillary contents are thoroughly examined by the clearing method described by Pickren.[5] All axillary nodes, large and small, can be readily identified by this method. At least 4 to 5 sections were made from each lymph node for histologic examination.

Result

In 121 patients treated by radical mastectomy, the number of axillary nodes removed ranged from 3 to 63 with a median of 22 and a mean of 23.4 per patient (Table 1).

In contrast, among the women undergoing modified radical mastectomy, total number of axillary nodes removed ranged from 6 to 77 with a median of 24 and a mean of 25.7 nodes in each mastectomy specimen. The difference in numbers of axillary nodes removed by radical or modified radical mastectomies was not statistically significant by *t*-test (P = 0.104).

Five-year survival followup is available for 121 radical mastectomy patients. Modified radical mastectomy series is more recent and the evaluation of disease recurrence somewhat less complete. The results, as shown in Table 2, disclose that the recurrence free survival in these two groups is comparable. Statistical analysis was done in both node negative and positive groups by Breslow life table test and no significant difference was found in either group (P = 0.44 for node negative group and P = 0.58 for node positive group).

TABLE 3. *Age and Nodal Status*

	Radical Mastectomy	Modified Radical Mastectomy
≤50	41	38
>50	80	71
0 nodes	53	45
1-3 nodes	34	30
4 + nodes	34	34

TABLE 4. *Skin Recurrences*

	Radical Mastectomy		Modified Radical Mastectomy	
Year	Negative nodes	Positive nodes	Negative nodes	Positive nodes
1	1/53	10/68	2/45	7/64
2	1/53	5/68	0/33	1/54
3	0/53	1/68	0/26	3/41
4	0/53	0/68	0/19	0/33
5	1/53	0/68	0/10	1/24

The data also show that composition of patients by age is similar in both groups (Table 3). No difference was noted in the extent of nodal metastasis in those two groups.

Table 4 summarizes the data on the frequency of skin recurrences in these two groups of patients. The results show that the incidence of local recurrence is about the same whether the surgical procedure is a Halsted radical or a modified radical mastectomy.

Discussion

The efficacy of the modified radical mastectomy must be measured by the curative achievement over a sufficient period of time. In this series, the duration of followup for most of the patients is still too short to allow any definitive conclusion. However, the analysis of recurrence-free survival and the incidence of skin recurrence thus far has failed to show a significant difference between the modified radical mastectomy and the Halsted radical mastectomy. Our study clearly shows that modified radical mastectomy can remove axillary lymph nodes as completely as radical mastectomy.

Involvement of pectoral muscles by tumors occurs only in advanced breast cancers and the removal of pectoral muscles perhaps is not an essential part of a curative mastectomy.[6] Our clinical experience demonstrates that a satisfactory surgical exposure of the axilla and a complete axillary dissection can be accomplished without removing the pectoralis major.

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Wound Infection in Colonic Surgery

ERDEN FIKRI, M.D., ANDREW J. McADAMS, M.D.

Three hundred forty-one consecutive cases of colonic surgery performed by the Proctology service of our hospital have been reviewed. There was a total of 7 wound infections, constituting an incidence of 2.1%. The infection rate in clean contaminated cases was 0.8% and in contaminated cases, 4.7%. The mortality rate was 2.3%. Parenteral antibiotics were used in less than 50% of the operations. Our impression is that attention to one modality of wound infection prevention with disregard for the others will produce little. However, close attention to all the modalities by which we can hope to reduce wound infection appears to produce strikingly beneficial results.

PRIOR TO THE USE of antibiotics the incidence of infectious complications in colonic surgery was well over 50%. The discovery of antibiotics was a giant step forward in the field of surgery and in the fight against infection. However, despite our present potent antibiotics, the incidence of wound infection in colonic surgery remains quite high, reported in the literature from 2.5%[1] to 20%.[2] It is doubtful whether this figure will change appreciably with the discovery of newer and more effective antibiotics. If we are to get better results, there is probably one area in which there is still room for improvement—and that is a re-consideration of our surgical technique.

Material and Results

This study is a review of 341 consecutive cases of colonic surgery performed by the Proctology service at The Western Pennsylvania Hospital during a 5-year period from January 1968 to December 1972. Two hundred and thirty-four operations were done for neoplastic disease and 107 for inflammatory disease. The latter consisted of 68 operations for diverticulitis and 39 operations for ulcerative colitis or granulomatous colitis.

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Table 1 shows the types of operations performed for the various inflammatory and neoplastic diseases of the colon. Resection for massive diverticular bleeding was considered an operation for inflammatory disease.

Any wound collection or drainage, other than a hematoma, with a positive culture was considered a wound infection.

There was a total of 7 wound infections out of 341 operations—an incidence of 2.1%. The number of wound infections in patients with neoplastic disease was 2—an incidence of 0.8%. The number of wound infections in patients with inflammatory disease was 5—an incidence of 4.7%. Table 5 shows the type of organism that was present in each case of wound infection.

Out of 305 clean contaminated cases, more than 50% received no pre–or postoperative parenteral antibiotics (Table 2). There were 5 wound infections in this group—an incidence of 1.6%. Of these, only 2 received parenteral antibiotics.

All of the 36 contaminated cases received parenteral antibiotics (Table 3). There were two wound infections in this group of which one received both pre and postoperative antibiotics and the other received antibiotics only after surgery.

Twenty-one patients had emergency surgery on an unprepared bowel (Table 4). There were two wound infections in this group. One was in a patient who was septic from a perforating diverticulitis with abscess formation; this patient had an emergency colostomy and drainage procedure. The other was in a patient who underwent

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TABLE 1. *Type of Resection*

Type of Operation	No.	No. of Operations for Neoplasm	No. of Operations for Inflammation	Emergency Operations	No. of Wound Infections	No. Receiving Pre- and Postop Antibiotics	No. Receiving only Postop Antibiotics
1. Colectomy a) Rt. Colectomy b) Lf. Colectomy c) Segmental Resection	98	71	27	3	1	20	15
2. Total and subtotal Colectomy (with Ileostomy or Ileorectal Anastomosis)	23	—	23	6	1	10	7
3. Low-Anterior Resection	89	58	31	3	2	21	26
4. A-P Resection	60	49	11	—	2	14	9
5. Colotomy and Polypectomy	42	42	—	—	—	—	3
6. Colostomy	29	14	15	9	1	11	5

colectomy with a transverse colostomy for an obstructing carcinoma of the proximal sigmoid colon.

There were 8 deaths, with an operative mortality of 2.3%. Four died of myocardial infarction with congestive heart failure, and one died of a massive stroke. Three patients died of sepsis from anastomotic breakdown. The average age of death was 76.

Each patient received a thorough mechanical and oral antibiotic bowel prep except the 21 patients who had emergency surgery on an unprepared bowel. Each patient was put on a low residue diet 72 hours before surgery. Forty-eight hours prior to surgery they were given 1.0 gm of Neomycin and 500,000 units of Mycostatin by mouth every 6 hours, and were started on a clear liquid diet. Thirty milliliters of Fleets phospho soda was given in the morning and a cleansing soapsuds enema in the evening. Twenty-four hours before surgery unobstructed patients were given cleansing soapsuds enemas in the morning and four dulcolax tablets by mouth in the evening. A liter of saline enema containing 2.5 gm of neomycin was also given the evening prior to surgery and in the morning of surgery.

All the operations were done by one surgeon and a fine atraumatic technique was used in every case. Impermeable pads were used to cover wound edges and other abdominal structures at the time of transection and anastomosis of the bowel to protect against spread of organisms from the transected bowel. An open anastomosis was performed in every case. Phenol and alcohol were applied to the transected edges of bowel immediately after transection to prevent contamination of the operative field. At the time of anastomosis these edges were cut and discarded. In every case a separate wound closure set was used in which gowns, gloves, and instruments were changed and the patient was redraped before abdominal closure. All extra-peritoneal tissue layers were irrigated with 500 cc of 1% neomycin solution during wound closure.

TABLE 2. *Clean Potentially Contaminated Cases: 305 Patients*

	No. of Patients
Parenteral antibiotics (postoperative only)	133 (43.6%)
Pre- and postoperative parenteral antibiotics	61 (20%)
Number of wound infections	5 (1.6%)

Discussion

Despite recent advances in colorectal surgery, the incidence of wound infection remains unacceptably high. In addition to the risk and suffering involved, prevention of wound infection is also economic when one considers the prohibitive added expense of prolonged hospitalization.

The importance of the endogenous origin of wound infection in colonic surgery has been well documented.[3–6] There is a significant association between bacteria isolated from the colon at surgery and those isolated from subsequent wound infection. In cases where *E. coli* has been cultured from the subcutis at closure, there was a subsequent wound infection with the same organism in more than 50%.[9]

TABLE 3. *Contaminated Cases: 36 Patients*

Number of patients receiving parenteral antibiotics (postoperative only)	36 (100%)
Number of patients receiving pre- and postoperative parenteral antibiotics	15 (42%)
Number of wound infections	2 (5.5%)

TABLE 4. *Emergency Operations on Unprepared Bowel (21 operations)*

Reason for Emergency Surgery		
Carcinoma	7	
Inflammatory Disease of Bowel	9	
Massive Colonic Hemorrhage	5	
Type of Surgery		
Colostomy (1 wound infection)	9	
Subtotal Colectomy With ileo-rectal Anastomosis	5	
Subtotal colectomy With ileostomy	2	
Procto-colectomy (1 wound infection)	2	
Low anterior Resection	2	
Number of Wound infections	2	(9.5%)

Control of wound infection in colonic surgery involves essentially the prevention of contamination which can be minimized by reduction of the total number of bacteria in the alimentary tract and by protecting the tissues mechanically by proper draping and chemically by appropriate parenteral or topical antibiotics.

Prevention of contamination of the abdominal wound is almost entirely technical and involves effective isolation of contaminated gloves, instruments, and drapes from contact with the abdominal wound. We use impermeable pads to cover wound edges at the time of transection and anastomosis of the bowel. A wound liner may be equally effective but is more expensive. In another series of cases, the use of adherent plastic skin drape was not helpful in reducing wound infections.[10]

Reduction of the total number of bacteria in the alimentary tract can be achieved by the use of oral laxatives, enemata, and oral antibiotics. The use of oral antibiotic bowel preparation is still controversial, the major objection being that it predisposes to the dreaded complication of enterocolitis.[7] We have not had this complication in our series. Some surgeons now use a short course (12-24 hours) of oral, nonabsorbable antibiotics.[9] This gives the benefit of reduced bacterial level in the bowel and also avoids the emergence of antibiotic-resistant virulent organisms in the colon.

Polk[8] has clearly demonstrated the efficacy of preoperative and short term postoperative parenteral antibiotics in preventing wound infection in potentially contaminated operations.

We believe that irrigation of all extraperitoneal tissue layers with 500 cc neomycin in saline solution during abdominal wound closure further reduces the incidence of wound infection. Anderson et al.[1] have reduced their wound infection rate in 120 colon cases from 18.3% to 2.5% in a triple blind study by the use of 1.0 gm of ampicillin powder in the wound. However, we feel that the mechanical cleansing obtained by flooding the wound is as important as the antibacterial effect of the antibiotic.

We feel that our low incidence of wound infection is not due to one single factor but due to close attention to all of the modalities by which we hoped to reduce wound infection. Finally, the importance of fine, atraumatic surgical technique cannot be overemphasized.

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TABLE 5. *Patients With Wound Infection (7)*

Patient	Type of Resection	Pathology	Type of Organism	Antibiotics (Parenteral)
1	Colectomy (E)*	Diverticulitis	Enterococci, E. coli	Pre- and postop
2	Subtotal Colectomy (EL)†	Ulcerative Colitis	E. coli, Enterococci	Only postop
3	Low anterior resection (EL)	Carcinoma	E. coli, Strepococci	None
4	Low anterior resection (EL)	Diverticulitis	E. coli, Enterococci	Only postop
5	A-P Resection (EL)	Ulcerative Colitis	Staph. epidermides	Pre- and postop
6	A-P Resection (EL)	Carcinoma	E. coli, Enterococci	None
7	Colostomy (E)	Diverticulitis	Enterococci, Proteus	Pre- and postop

*E = Emergency.
†EL = Elective.

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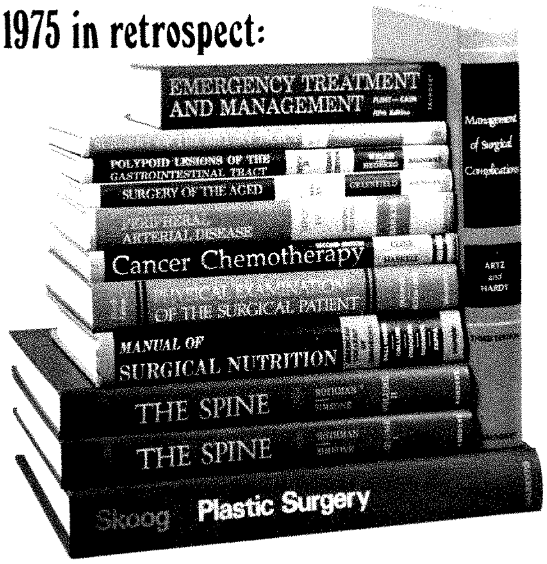
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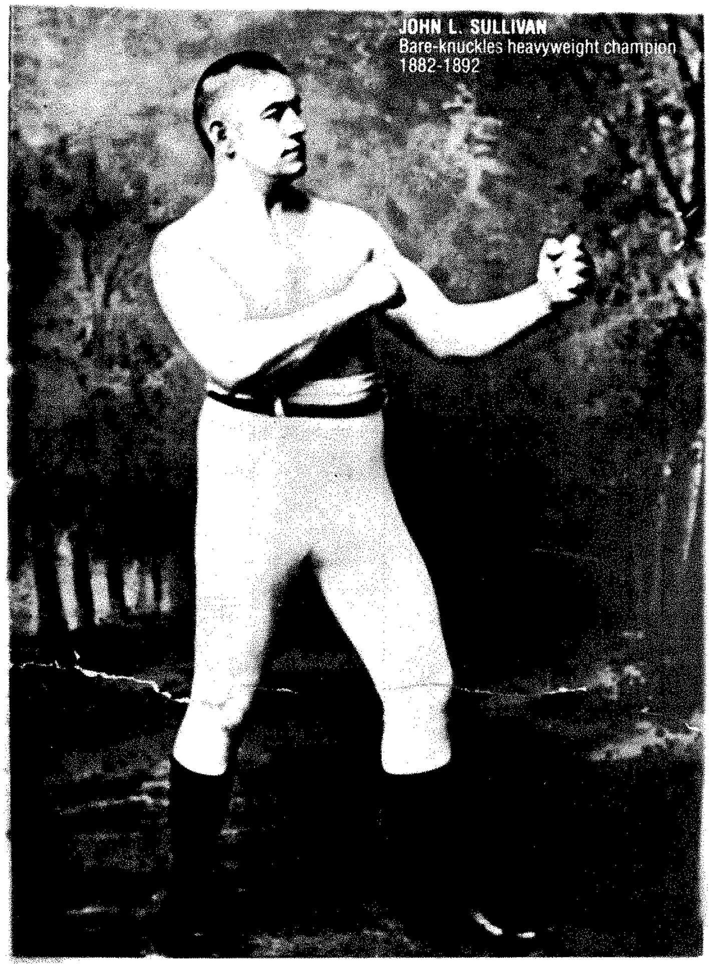

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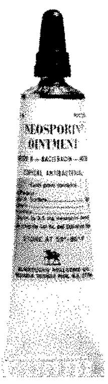

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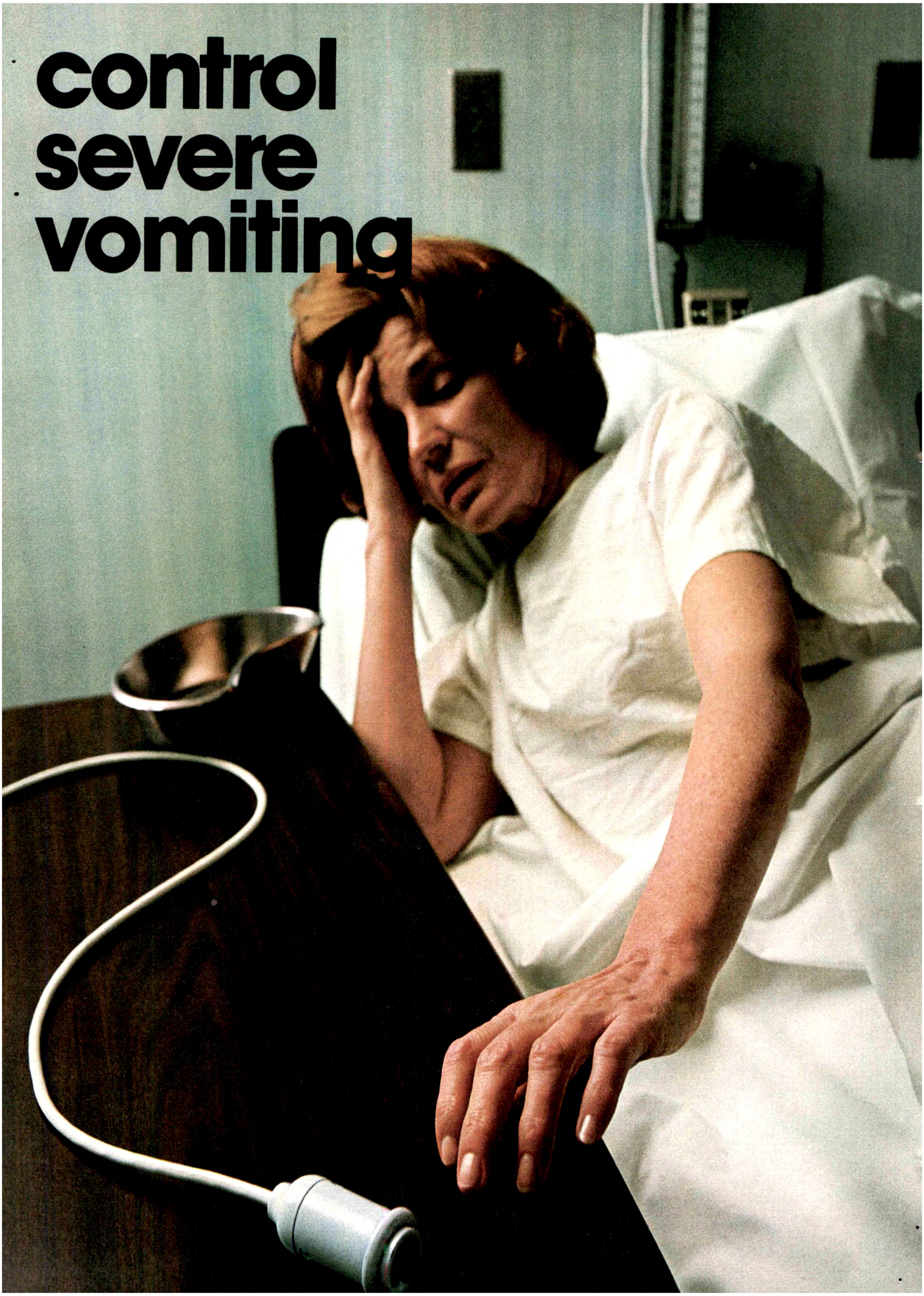

control
severe
vomiting

Unsurpassed antiemetic action helps restore normal digestive function so postoperative recovery can proceed smoothly.

11 dosage forms and strengths permit easy administration by parenteral, rectal or oral routes.

'Compazine' is contraindicated in pediatric surgery and in greatly depressed states due to C.N.S. depressants.

The possibility of postoperative aspiration of vomitus should be borne in mind.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: To control severe nausea and vomiting. For the management of the manifestations of psychotic disorders.

Possibly effective: To control excessive anxiety, tension and agitation as seen in neuroses or associated with somatic conditions.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings: Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: Antiemetic effect may mask toxic drug overdosage or physical disorders. Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. **In children with acute illnesses or dehydration, use only under close supervision.**

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

Supplied: Tablets—5, 10 and 25* mg., in bottles of 100; Spansule® capsules—10, 15, 30 and 75* mg., in bottles of 50; Injection—5 mg./ml.; Suppositories—2-1/2, 5 and 25 mg.; Syrup—5 mg./5 ml.; Concentrate (intended for institutional use only)—10 mg./ml.; Single Unit Packages of 100 (intended for institutional use only)—5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

*For severe neuropsychiatric conditions.

Compazine®

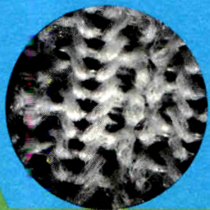
Injection 5 mg./ml.

brand of
prochlorperazine

the emesis nemesis

Smith Kline & French Laboratories SK&F
Division of SmithKline Corp., Phila., Pa. 19101

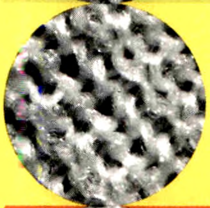
Because tubular design provides proper graduated compressio



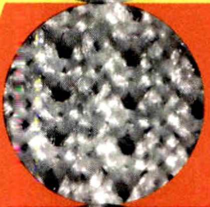
The knit is looser at the proximal end of the Zimmer anti-embolism stocking to accommodate the large circumference of the thigh without tourniquet effect. A unique thin foam lining and insert* helps keep the stocking up even when the patient is ambulatory.

The open knit above the knee exerts minimal compression so it will not inhibit blood flow being forced through the venous system by tighter compression distally on the leg.

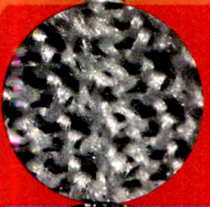
The knit loosens significantly at the knee to minimize pressure on the popliteal vein.



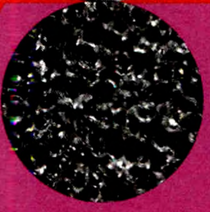
The tight knit over the calf forces the blood into the deep system while it compresses the superficial veins.



The knit is tightest at the ankle to provide the greatest compression distally.

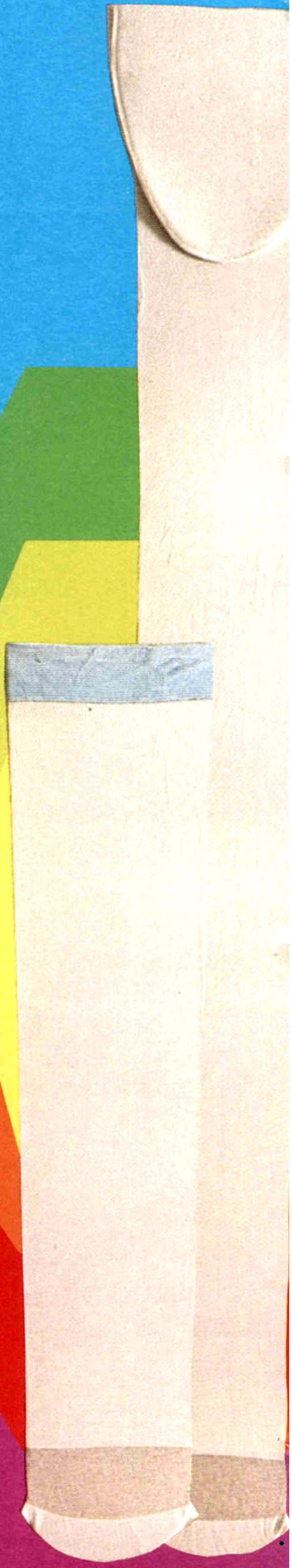


A wide band of lighter knit material facilitates easy application of the stocking and proper fit around the heel and instep.



The transparent toe window allows a quick check of blood circulation without removing or adjusting any portion of the stocking.

* Patents Applied For



the new Zimmer anti-embolism stocking

PATENTS APPLIED FOR

Correct graduated compression is now controlled by a single variable – the tightness of the stitch at a given circumference.

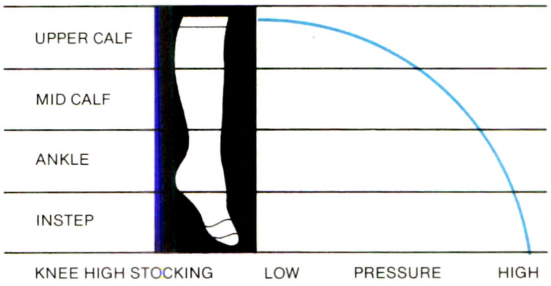
The new tubular design anti-embolism stocking from Zimmer·USA precisely controls compression through the amount of elasticity knitted into the stocking. This unique variable knit* is precisely controlled during manufacture with sophisticated, programmable knitting machines. Because precise control is exercised over the knit at any circumferencial point on the leg, the Zimmer anti-embolism stocking provides gradually decreasing pressure that enhances the venous return mechanism. Tightness of the knit is the key factor controlling the amount of compression.

*Patents Applied For

It shapes itself to fit virtually any leg.

Because no two legs are exactly alike, any pre-shaped anti-embolism stocking may not exactly match the contours of an individual patient's legs. Improper fit could cause constriction at some point on the leg. The stocking's tubular design adapts itself to even slight variations in the contour of a patient's legs and provides correct graduated compression through its built-in graduated elasticity. Available in many size and style combinations — 36 in all — to assure a correct fit for virtually any patient.

GRADUATED COMPRESSION CURVE



CLINICAL REFERENCES available on request from Zimmer•USA.

CONTRAINDICATIONS: Do not use in the presence of potentially compromised vascular circulation, i.e.: arteriosclerosis, congestive failure, massive edema, etc. Not recommended for use in the presence of open skin lesions or disease. Do not use over the thigh when the thigh circumference is greater than 28".

WARNING: Use proper size of stocking for the patient. Be sure heel is placed in the heel instep band. Discontinue use if circulation is compromised as indicated by pain, loss of capillary pulse in toes, etc. Do not roll down the top of stocking as a tourniquet effect may occur. CAUTION: Federal law restricts this device to sale by or use on the order of a physician.

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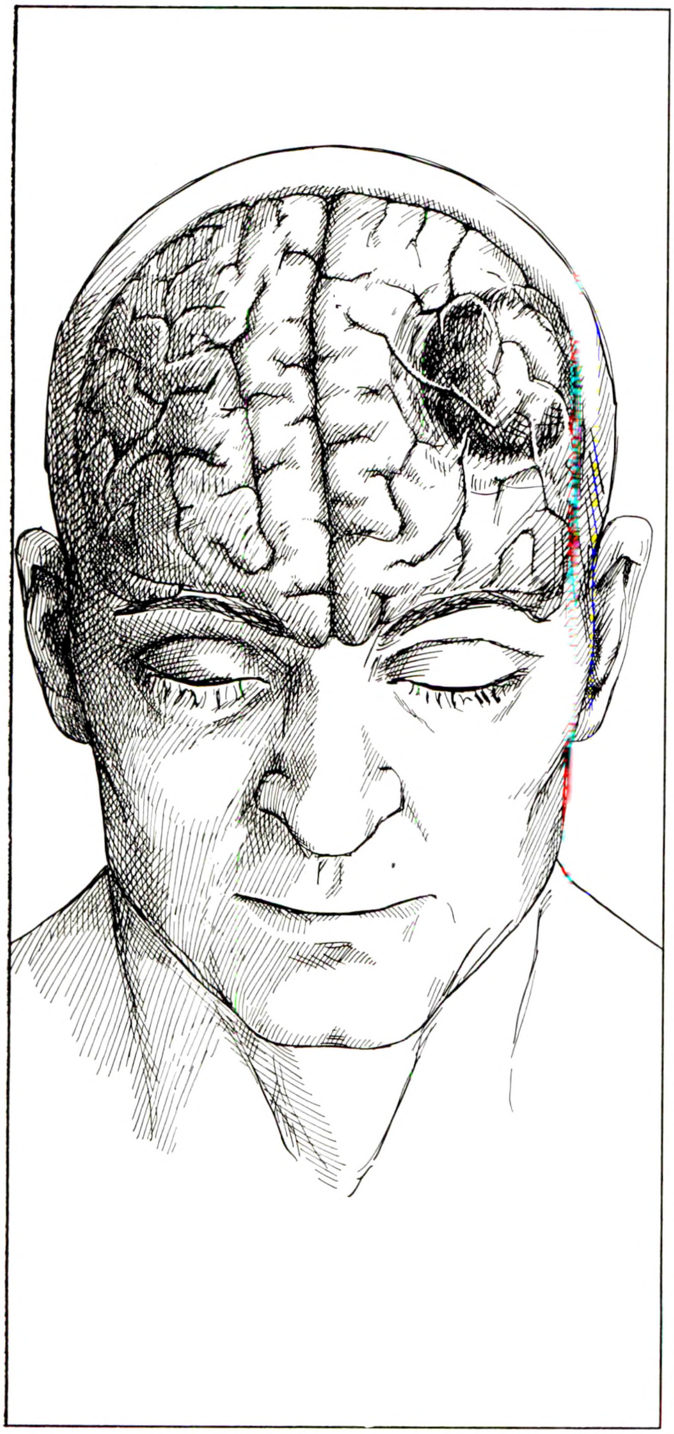
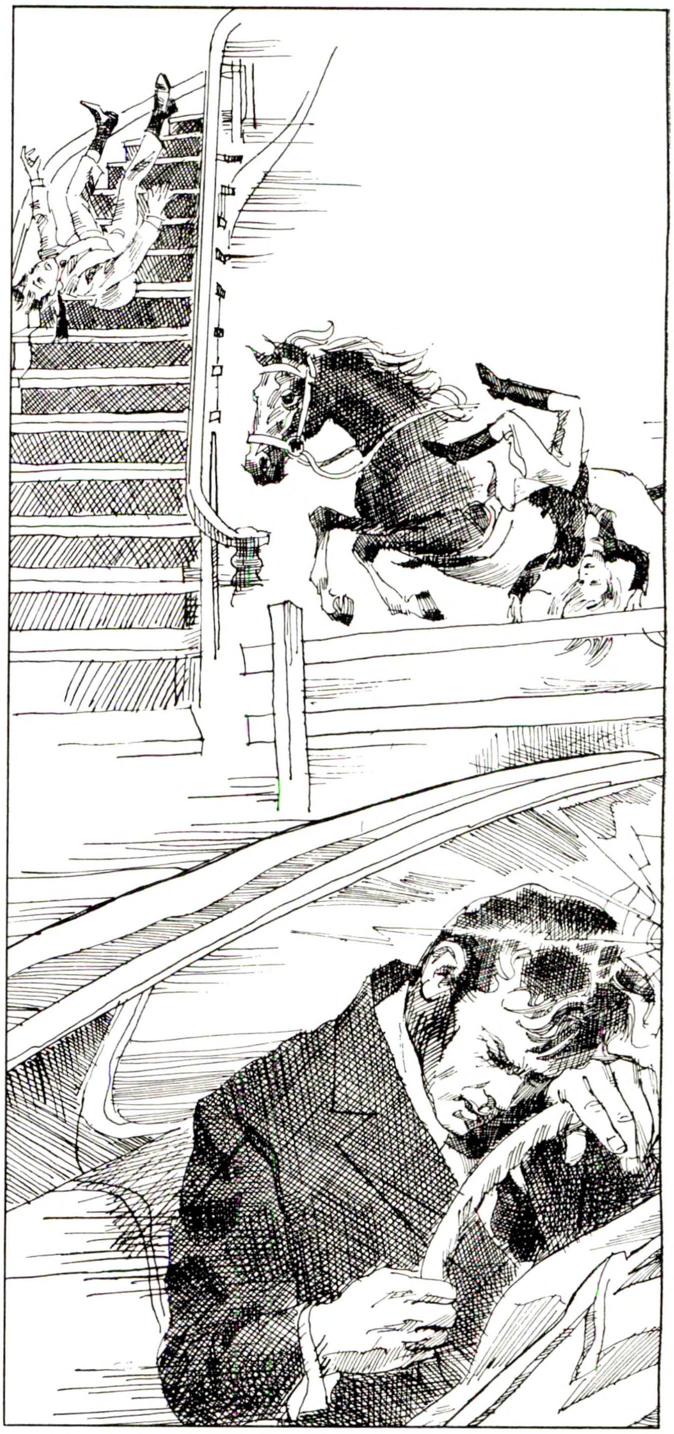
cerebral

expect it as a possible complication of primary or metastatic brain tumor.



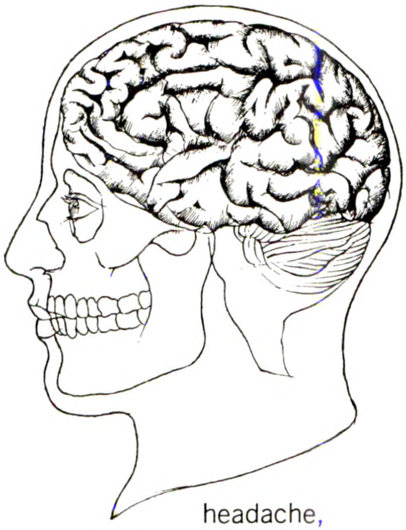
expect it in the presence of severe head injury.



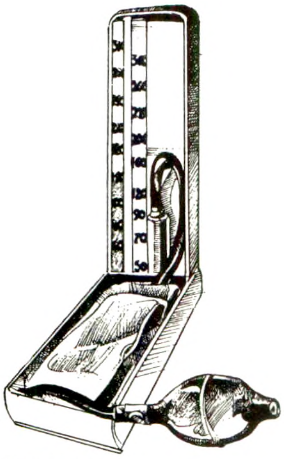
edema*

suspect it in the presence of signs and symptoms such as these:

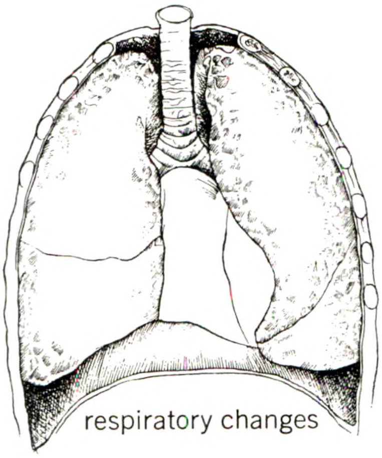
projectile vomiting



headache, altered consciousness



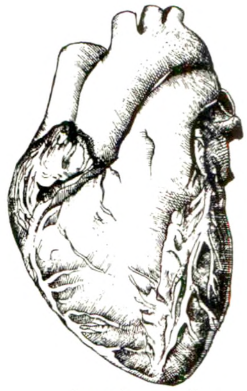
increased blood pressure



respiratory changes

dilated pupil, papilledema,

unilateral or bilateral abducens palsy



bradycardia

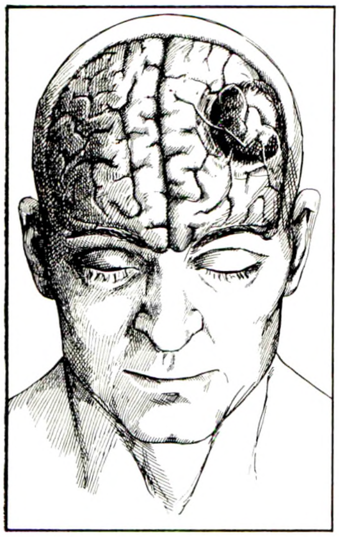
***Note: The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.**

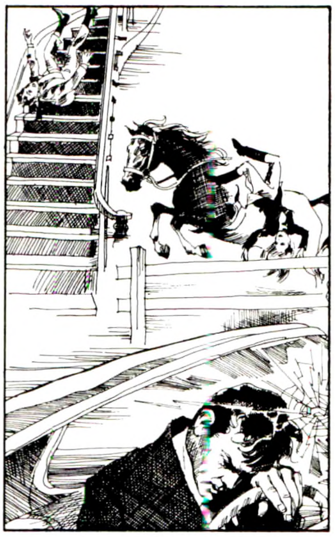
Injection:
4 mg/ml
Phosphate

Tablets:
4 mg, 1.5 mg, 0.75 mg, 0.5 mg, 0.25 mg

an indication for **DECADRON**® (Dexamethasone Sodium Phosphate | MSD) and **DECADRON**® (Dexamethasone | MSD)

For a brief summary of prescribing information, please see following page.





Injection Decadron® Phosphate

(Dexamethasone Sodium Phosphate|MSD)

"Some degree of edema accompanies most head injuries. Various methods have been used to control this, but at present the most efficient method is use of ... dexamethasone [DECADRON®]. . . .The effect of this is not well understood, but there is little question that edema of the brain is significantly lessened by its use."

Ritchie WP: The emergency care of cerebral injuries, J Lancet *86:*255, June 1966.

The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

Dosage for cerebral edema

Injection DECADRON Phosphate is generally administered initially in a dosage of 10 mg dexamethasone phosphate (2.5 ml) IV followed by 4 mg dexamethasone phosphate (1 ml) IM every six hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For the palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy should be individualized with either Injection DECADRON Phosphate or Tablets DECADRON (supplied as 4.0-, 1.5-, 0.75-, 0.5-, and 0.25-mg tablets). Two mg two or three times daily may be effective. The smallest dosage necessary to control cerebral edema should be utilized. The usual precautions in regard to corticosteroid therapy should be employed, and antacids, anticholinergic drugs, and diet measures to prevent gastrointestinal ulcer or hemorrhage should be considered. Please read the brief summary below, and consult full prescribing information before prescribing or administering.

Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction; hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

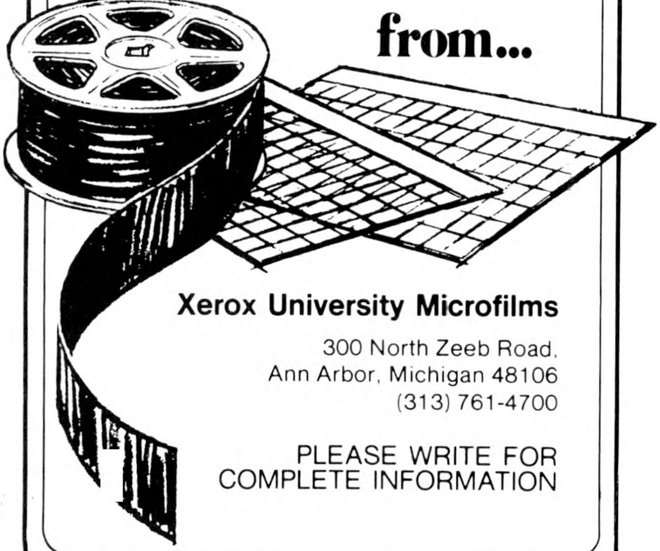
How Supplied: Tablets in five strengths: 4 mg dexamethasone, in bottles of 50 and single-unit packages of 100; 1.5 mg dexamethasone, in bottles of 50; 0.75 mg dexamethasone, in 5-12 PAK® (package of 12), single-unit packages of 100, and bottles of 100 and 1000; 0.5 mg dexamethasone, in bottles of 100 and 1000; and 0.25 mg, in bottles of 100. Injection, in 1-ml disposable syringes and 1-ml, 5-ml, and 25-ml vials, containing per ml: dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone, 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, water for injection q.s. 1 ml, and 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

Tablets
DECADRON®
(Dexamethasone|MSD)

Injection Phosphate
DECADRON®
(Dexamethasone Sodium Phosphate|MSD)

MSD
MERCK
SHARP&
DOHME



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Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Tigan is indicated for the control of nausea and vomiting.

CONTRAINDICATIONS: The injectable form of Tigan in children, the suppositories in premature or newborn infants, and use in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.

WARNINGS: Tigan may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. Reye's Syndrome has been associated with the use of Tigan and other drugs, including antiemetics, although their contribution, if any, to the cause and course of the disease hasn't been established. This syndrome is characterized by an abrupt onset shortly following a nonspecific febrile illness, with persistent severe vomiting, lethargy, irrational behavior, progressive encephalopathy leading to coma, convulsions and death.

Usage in Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or stillborn pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.

PRECAUTIONS: During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

HOW SUPPLIED: Ampuls, 2 ml, boxes of 10. Multiple Dose Vials, 20 ml. Thera-Ject™ (Disposable Syringes), 2 ml, boxes of 10.

Many things have changed in the operating room in 15 years..

but the Tigan effect hasn't.

(trimethobenzamide HCl)

When Tigan was introduced in 1959, nausea or vomiting was a frequent post-operative occurrence. Advances in surgical technique and anesthetic agents have reduced these incidences. However, when you need control of emesis and need it quickly, Tigan provides the necessary effectiveness with a relative lack of side effects.

Tigan has been used successfully with many different anesthetics and in all types of surgery without potentiating the anesthesia, delaying the awakening or altering the patient's vital signs (although a few instances of hypotension have been reported).

Beecham
laboratories, Bristol, Tennessee 37620

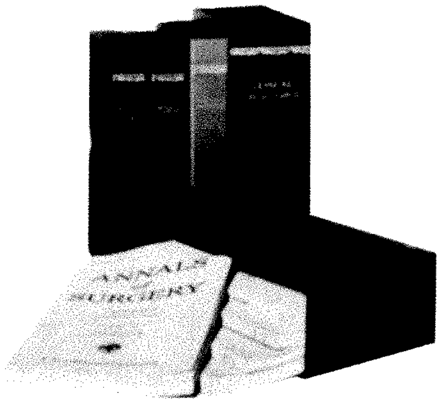
Tigan Injectable is intended for intramuscular administration only: the recommended adult dose—2 ml. (200 mg.) t.i.d. or q.i.d. (It is contraindicated in children)

For prompt control of nausea and vomiting

Tigan® Injectable

(trimethobenzamide HCl)

Please see adjoining page for Brief Summary.



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DARVOCET-N® 100
propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

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propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

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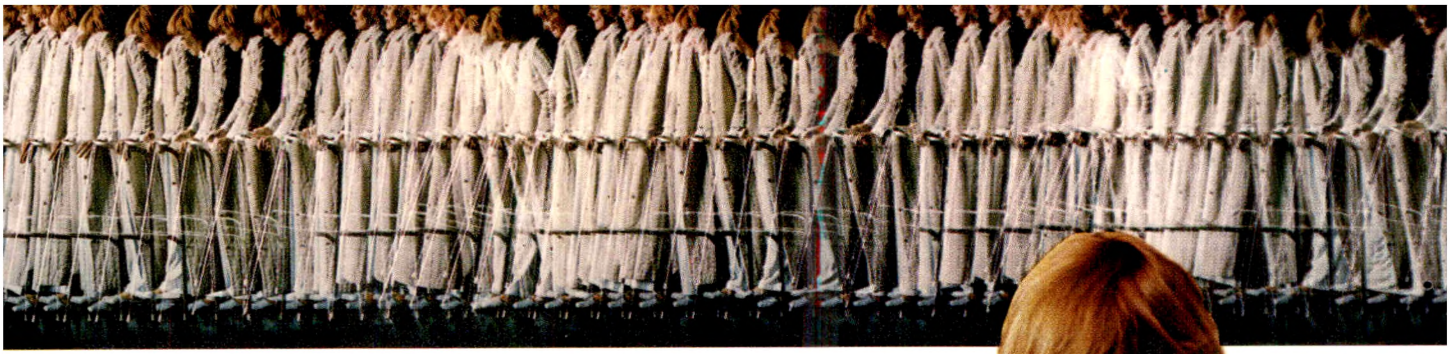

Relief from her postsurgical pain

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100 mg. propoxyphene napsylate and
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65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
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See summary of prescribing information on adjoining page.

The local that gives you the longest anesthesia gives your patient longer postoperative analgesia.

Marcaine® (Brand of bupivacaine hydrochloride) is the local anesthetic that provides the longest duration of action among commonly used local anesthetics. Which minimizes the problems during "continuous" technique or repeat doses.

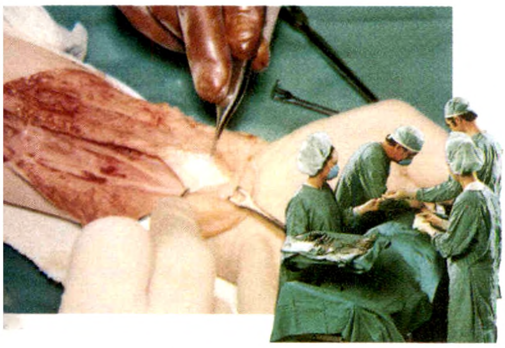
Marcaine also provides the longer postoperative analgesia. Which reduces the need for postoperative narcotics.

And in data in over 3,000 patients, Marcaine was reported to have excellent or satisfactory results in more than 96% of cases.

Extended anesthesia for the surgeon

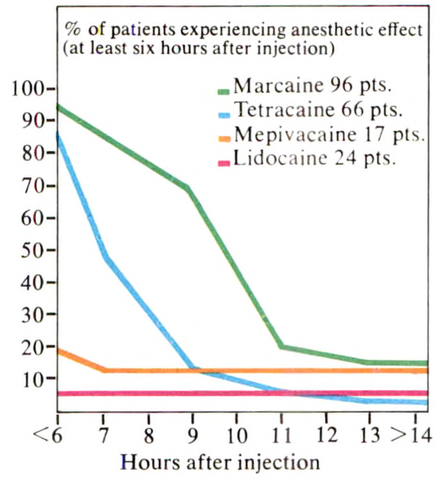
In regional blocks, Marcaine usually provides anesthesia at least 1½ to 2 times longer and occasionally even longer than lidocaine or mepivacaine. And approximately 20% longer than tetracaine. As established in several thousand surgical and obstetrical patients.[1-5]

In fact, a single Marcaine injection may be enough for up to 3½ hours of anesthesia for surgery,[5,6] and often provides analgesia that carries over into the recovery room and beyond.[8] When necessary, doses may be repeated up to once every three hours. Caution is advised in administration of repeat doses to patients with severe liver disease. Until further experience is gained, total daily dose of 400 mg. should not be exceeded nor is administration to children under 12 recommended.



This longer anesthetic action can minimize problems during "continuous" technique or repeat doses. Thus, there is the further advantage of a reduced likelihood of introducing infection since injections are less frequent.

Chart I
Duration of anesthesia
Percentage of patients experiencing anesthetic effect—
Comparison of Marcaine and other local anesthetics*



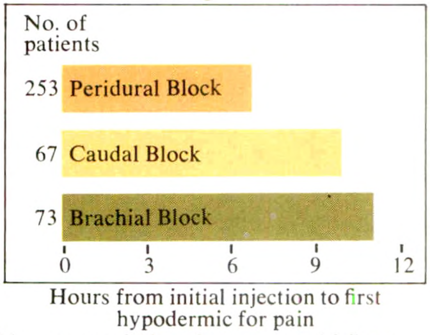
*Equipotent doses used for bilateral, simultaneous blocks of sciatic/femoral, intercostal, or brachial/axillary nerves. Adapted from Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute.

Extended postoperative analgesia for the patient

Marcaine gives your patient more—considerably more—post-anesthetic analgesia than other local anesthetics in various types of nerve blocks.[3,5,8,10] An analgesia that persists after the return of sensation. As a result, you may be able to defer,[1,6] and sometimes even eliminate,[6] postoperative narcotics. The table above right illustrates the average duration of time between the initial Marcaine injection and the need for post-op analgesics.

As can be seen in Chart II, many of the 67 patients given Marcaine with epinephrine caudally for rectal surgery did not complain of pain for 12 hours or longer following induction. In another group of 40 patients[10] given Marcaine or mepivacaine locally for tonsillectomy, Marcaine pain relief lasted 3 to 5 times longer than that provided by mepivacaine. And in a study[1] of 84 patients given Marcaine caudally for perineal surgery, complete sensation returned in approximately 8½ hours for the average patient. And the majority of patients did not require a narcotic for an additional 1 to 3 hours.

Chart II
Duration of time between injection of Marcaine and need for postop analgesics†



†Average—exclusion of extremes and failures. Adapted from Lund, P.C., *et al.*: *Anesth. Analg.* *49*:103, Jan.-Feb. 1970.

Excellent clinical acceptance

Marcaine was administered to 3,112 patients for various types of local anesthesia.[11] Of these patients, only 2 experienced a systemic reaction. Although Marcaine has a very wide safety margin, adverse reactions characteristic of those associated with other amide local anesthetics may occur.

Marcaine is indicated for most anesthetic blocks; however, until further clinical experience is gained, paracervical block is not recommended.

See important product information concerning warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations on next page.

Extends the limits of time in anesthesia [1-5]
Extends the limits of time in postoperative analgesia [3,5,8,10]

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One local does both

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MARCAINE® Hydrochloride
Brand of **bupivacaine hydrochloride**

Actions: Parenteral administration of Marcaine stabilizes the neuronal membrane and prevents initiation and transmission of nerve impulses, thereby effecting local anesthetic action.

Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used, to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each repeated dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine (bupivacaine hydrochloride) should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation. Other causes of reactions to these local anesthetics may be hypersensitivity, idiosyncrasy, or diminished tolerance.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest.

Allergic reactions are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

In obstetrics, cases of fetal bradycardia have occurred.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium, such as ephedrine and metaraminol).

Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate or muscle relaxant, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or a short-acting muscle relaxant (succinylcholine). Intravenous muscle relaxants and barbiturates should only be administered by those familiar with their use.

References: 1. Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine, a review of 2,077 cases, *J.A.M.A. 214*:713, Oct. 26, 1970. **2.** Moore, D. C., Bridenbaugh, L. D., Bridenbaugh, P. O., *et al.*: Bupivacaine for peripheral nerve block: a comparison with mepivacaine, lidocaine and tetracaine, *Anesthesiology 32*:460, May 1970. **3.** Hollmen, A.: Axillary plexus block: a double-blind study of 59 cases using mepivacaine and LAC-43, *Acta Anaesthesiol. Scand., Suppl. 21*:53, 1966. **4.** Herbring, B. G.: A comparative study of LAC-43, mepivacaine and tetracaine in caudal anesthesia, *Acta Anaesthesiol. Scand., Suppl. 21*:45, 1966. **5.** Bromage, P. R.: A comparison of bupivacaine and tetracaine in epidural anesthesia for surgery, *Can. Anaesth. Soc. J. 16*:37, Jan. 1969. **6.** Lund, P. C., Cwik, J. C., and Vallesteros, F.: Bupivacaine—a new long-acting local anesthetic agent, a preliminary clinical and laboratory report, *Anesth. Analg. 49*:103, Jan.-Feb. 1970. **7.** Ekblom, L. and Widman, B.: A comparison of the properties of LAC-43 prilocaine and mepivacaine in extradural anaesthesia, *Acta Anaesthesiol. Scand., Suppl. 21*:33, 1966. **8.** Moore, D. C.: Data in the files of the Sterling-Winthrop Research Institute. **9.** Wise, G. F.: Guest Discussion, *Anesth. Analg. 49*:113, Jan.-Feb. 1970. **10.** Puento-Egido, J. J., Dudeck, J., and Nolte, H.: The clinical use of the local anesthetic agent Marcaine (Carbostesin®), *Anaesthesist 16*:224, August 1967. **11.** Data in the files of the Sterling-Winthrop Research Institute.

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Extends the limits of time in postoperative analgesia[3,5,8,10]

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(1664M)

Preserved Allografts of Dilated Saphenous Vein for Vascular Access in Hemodialysis:

An Initial Experience

V. A. PICCONE, JR., H. LEE, S. RAMOS, N. AHMED, V. DISCALA,
M. HAMANCI, V.A. PICCONE, III, E. NIELSEN, H.H. LEVEEN, E. BERGER

Arteriovenous fistulas constructed from preserved (frozen) allograft veins provided vascular access for maintenance hemodialysis in 14 patients with inadequate vasculature for conventional autogenous fistulas. Electromagnetic flows ranged from 200 to 250 cc/min. Dialysis flows of 200 cc/min were accomplished consistently. The allografts were useable for dialysis much earlier than autogenous A-V fistulas. Arteriography demonstrated a wide vasculature channel very suitable for dialysis needles. Allografts seemed superior to bovine heterografts in both patency and susceptibility to infection. Scanning electron microscopy revealed smoother intimal surfaces if the donor received small amounts of heparin systemically while the veins were being removed. Allograft veins appear to be a useful alternative means of vascular access for hemodialysis.

IN THIS SECOND DECADE of maintenance hemodialysis therapy, vascular access has emerged as a major problem. Many patients experience failure of a primary arteriovenous fistula due to thrombosis, infection, trauma from dialysis needles, and progressive vascular diseases. Repeated construction of new fistulas systematically depletes conventional access sites in long surviving patients. Extension of the indications for dialysis, to include the elderly with their more diseased arteries, has complicated the vascular access problem even further. The many vascular procedures devised [1,2,4,6,9] to provide access reflect the extent of the problem and the innovative maneuvers of the vascular surgeon.

From the Departments of Medicine and Surgery, Brooklyn Veterans Administration Hospital and State University of New York, Downstate Medical Center and The Department of Medicine, United States Public Health Hospital, Staten Island, New York

Bovine heterografts,[4] mandril-grown grafts,[1] dacron velour prostheses[5] and a variety of autogenous vascular maneuvers[6] allow vascular access when standard Brescia-Cimino fistulas are not possible. However, the fibrous capsule which forms around the mandril requires time to develop,[1] thrombosis may occur on the dacron velour when the dialysis needle separates the neointima, and bovine heterografts frequently become thrombosed[11] or infected.[11] The renewed interest in vein allografts to bypass diseased peripheral arteries[9,11] and the low incidence of thrombosis in the renal veins of transplanted kidneys,[6] suggested allografts as an additional material for constructing arteriovenous fistulas. Schwartz[13] attributed a relatively weak antigenicity to vein allografts. The high flow and low pressure in A-V fistulas might theoretically indicate a lessor tendency toward thrombosis and aneurysm formation than when arterial homografts were used in arterial replacement or bypass.

The present study describes an initial experience with preserved allografts of dilated saphenous vein as a material for arteriovenous fistulas. The allografts have been

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used as venous segments of an A-V fistula and as superficial arterio-arterial bypass segments suitable for direct puncture.

Method

Arteriovenous fistulas were constructed from preserved allograft veins when superifical veins and/or arteries, which were patent and of adequate size, were unavailable. Fourteen patients received allograft veins. Most of the allografts were from donors with major blood groups dissimilar to that of the recipient because of the persistent shortage of allografts in the vein bank. This was contrary to original intent. The work of Ochsner suggests longer patency of vein allografts with major blood group compatability between donor and recipient.[12] Veins from donors with a major blood group dissimilar to that of the recipient were not used in renal transplant candidates. Several configurations included: 1) a straight line from the radial artery inflow to the first large open vein near the elbow (Fig. 1) and 2) a shallow curve from the distal brachial artery outward over the biceps and back into the proximal brachial vein. The first patterns was preferred because autogenous veins grafted in a straight line pattern remained patent longer than veins placed in the loop configuration.[6] Anticoagulation with heparin was maintained for the first two weeks to minimize the chance of thrombosis while neointima replaced any intimal slough in the allograft. Anastomoses were performed with 6-0 monofilament nylon without optical magnification after topical application of papaverine to the recipient's vessels. The allografts were passed through a subcutaneous tunnel by using a bronchoscope and biopsy forceps. This maneuver minimized twisting and provided a tunnel of proper diameter.

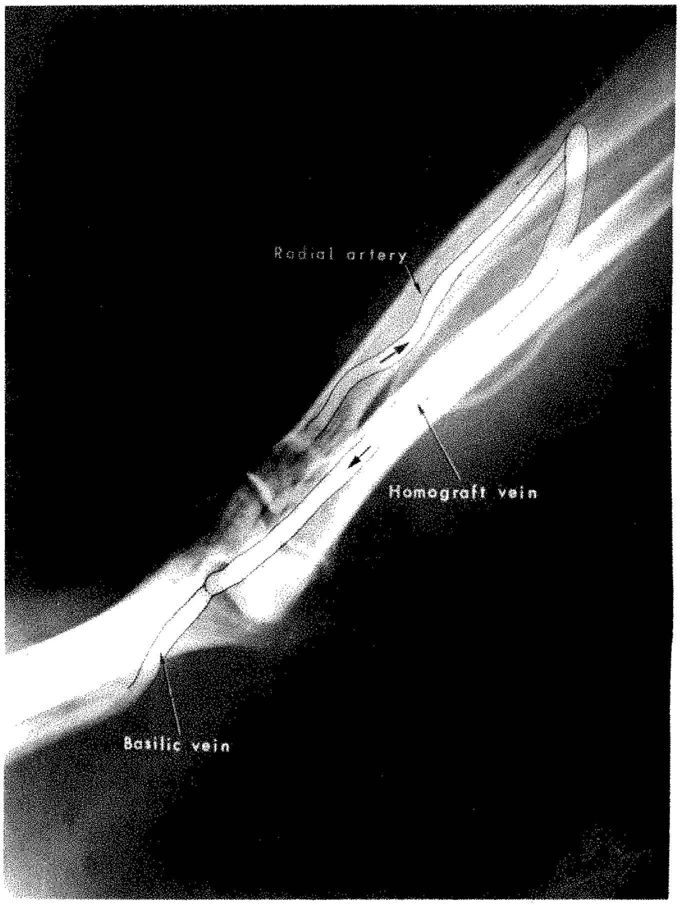


FIG. 2. Arteriogram demonstrates allograft vein from the origin at the radial artery to the upper anastomosis into the basilic vein. Outline of vessels is inked in because vessels did not contrast well against the radius in photographic prints.

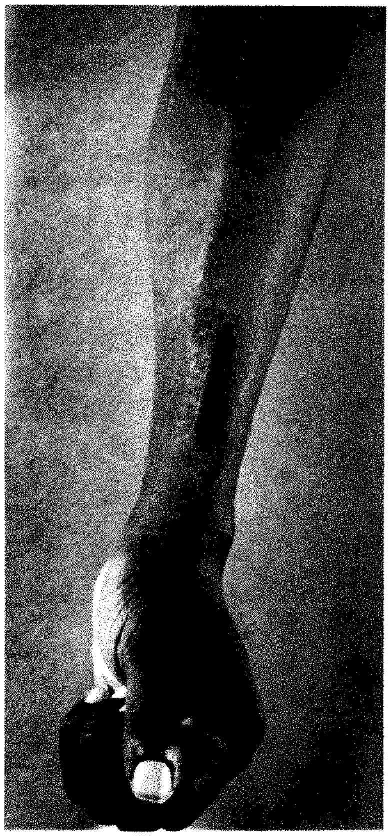


FIG. 1. Highlighted photograph of allograft vein for arteriovenous fistula demonstrates the straight line configuration from the radial artery to basilic vein and provides an appreciation of the ease with which these large vessels are cannulated for dialysis.

Blood flow through the allografts was measured with a Statham Model SP 2200 electromagnetic flowmeter with non-occlusive flow probes.

Veins were acquired from patients undergoing surgical treatment of varicose veins. The segment of long saphenous vein from the knee to the fossa ovalis was removed through multiple small incisions and prepared similar to

TABLE 1. *Electromagnetically Determined Blood Flow in Allograft Fistulas*

Patient	cc/min
G.D.	250
S.W.	250
M.E.	225
M.M.	250
R.G.	200

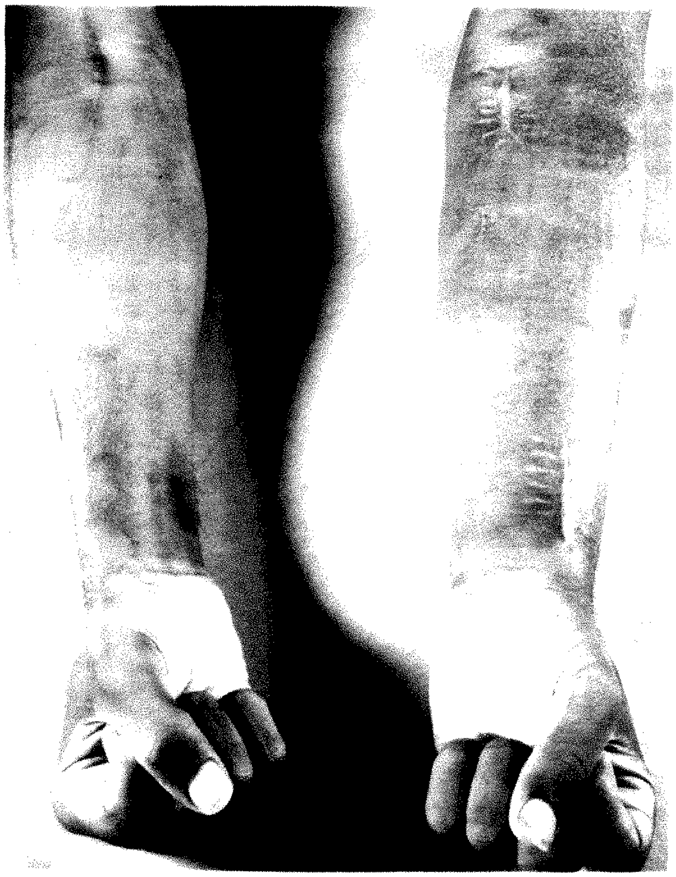


FIG. 3. Dialysis could be performed easily in spite of the extensive early edema which developed about this allograft. A biopsy performed close to the vein graft to examine the cellular changes associated with the edema was lost, but the technique will be valuable in studying host response to the frozen allografts.

veins used for aorto-coronary bypass grafts. Blood was washed from the veins with a solution of cold heparin and saline and the veins were placed in sterile plastic containers containing streptomycin and penicillin. A label indicated the donor's name, blood type, date of acquisition, length of vein segment, diameter of proximal lumen and diameter of distal lumen. After removal of a tiny segment for scanning electron microscopy and intimal protein absorption studies, the veins were stored at −40 C. The storage technique followed the description of Tice.[14]

Results

Fourteen dialysis patients received allograft arteriovenous fistulas from December, 1973 to February, 1975. All of the patients had severe vascular access problems. The 14 grafts were patent initially. None of the grafts became infected. One graft from a donor with a dissimilar major blood group became thrombosed several weeks after surgery. Angiograms consistently demonstrated a vascular channel which immediately after surgery was already the size of the mature A-V fistulas constructed from autogenous arm veins. Electromagnetically determined flows, shown in Table 1, were consistently high. The rapid flow of a wide column of blood guaranteed adequate inflow into the dialysis unit. The use of "unipuncture" needles sometimes necessitated application of topical thrombin at the puncture site. Grafts used for dialysis in as little as one day after surgery in three patients yielded an average flow of 250cc/min through the dialysis machine. Use of the grafts before fibrous attachment of the vein to the walls of the subcutaneous tunnel resulted in severe bleeding from the graft into the tunnel on two occasions. Once the vein had been ripped by the dialysis needle. Operative repair was required in both instances and dialysis (using the allograft) was deferred thereafter till the end of the first postoperative week.

Short term problems also included (1) moderate edema adjacent to the allografts in two patients and (2) closure of the inflow artery in one patient. The edema (Fig. 3) was sufficiently extensive to warrant elevation of the arm and elastic bandages for the first week and some edema persisted for over 6 weeks.

The one early failure was due to closure of the arterial

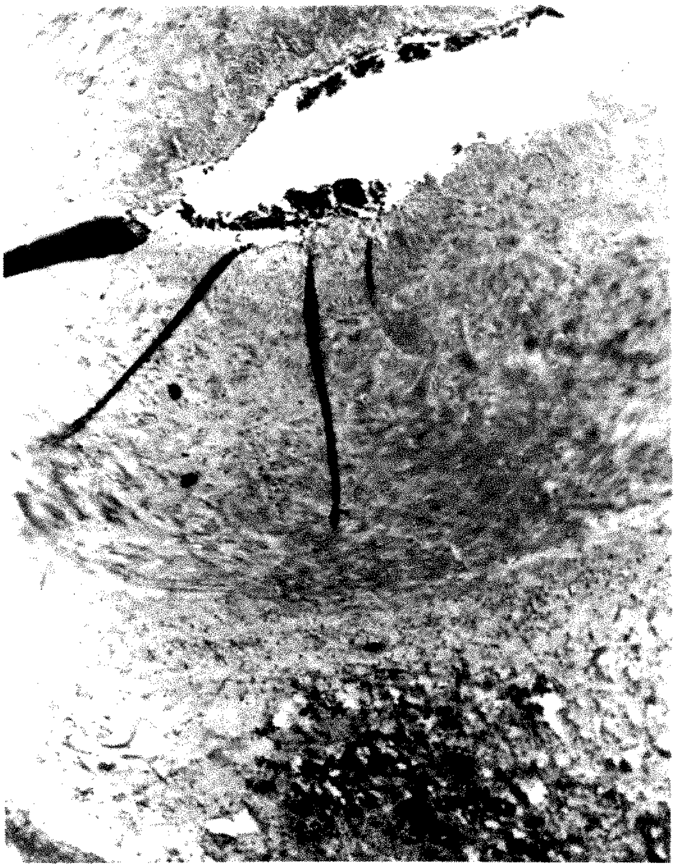


FIG. 4. Severe subintimal proliferative changes and thrombosis closed the inflow artery to one allograft. The diseased section of artery was resected and the end of the remaining artery was re-anastomosed to the allograft fistula. Similar arterial changes closed the inflow vessel again six months later.

TABLE 2. *Graft Size, Patency, and Suitability for Dialysis of Allograft Fistulas and Bypass Grafts (For Patients with Known Inflow and Outflow Diameters).*

Patient	Inflow Diameter (cm)	Outflow Diameter (cm)	Patency	Suitability for Dialysis
G. D.	1.0	1.2	Patent	200 cc/min with double needles no venous resistance
S. W.	1.1	1.3	Patent	200 cc/min with unipuncture no venous resistance
J. M.	1.0	1.2	Patent	200 cc/min with double needles no venous resistance
R. G.	0.9	1.1	Arterial inflow vessel failed and new inflow was established	200 cc/min with unipuncture venous resistance over 100 mm Hg
M. R.	0.8	0.8	Patent	200 cc/min with double needles low venous resistance
J. J.	1.1	1.3	Patent	200 cc/min with double needles low venous resistance
W. J.	0.7	0.9	Patent	200⁺ cc/min with unipuncture low venous resistance
D. G.	0.3	0.4	Patent	175-200 cc/min with double needles venous resistance unknown
C. S.	1.1	1.2	Patent	200⁺ cc/min with unipuncture low venous resistance
M. E.	0.9	1.0	Arterial bypass configuration-subintimal proliferation occluded vessel at 6 mos	150-200 cc/min high back pressure in venous line
M. E.	1.0	1.1	Patent	200 cc/min with double needles no venous resistance

inflow vessel and the vein allograft contained only liquified clot when the area was explored to determine the cause of the failure and to re-establish flow. The diseased artery is shown in Fig. 4 where a cross section demonstrates severe thickening almost totally closing the arterial lumen. A new inflow to the graft was established successfully by excising the narrowed portion of the artery and performing a new anastomosis. The same phenomenon occurred 6 months later and was again corrected.

Ten patients with arteriovenous fistulas have been followed closely (Table 2). None of the patients showed signs or symptoms of peripheral ischemia. Late complications have not appeared. All patients are being dialized from the allografts at up to one year after surgery. No secondary surgical procedures have been required for problems in the allografts. Undoubtedly, thrombectomies will eventually be done and resection of false aneurysm may be anticipated. The high success rate of the allograft fistulas was especially rewarding since most of the patients had repeated failure of other techniques for establishing vascular access or no veins of their own thus obviating the standard subcutaneous fistulas. The allografts most easily used for dialysis were those with the largest diameter. Narrow lumen veins from the patients without varicosities, those best suited for coronary bypass grafts, are poorly suited for dialysis. The saphenous vein is thick walled compared to an arm vein, does not become dilated rapidly, and may undergo subintimal proliferative changes. The greater saphenous vein from the patient with varicose veins is considerably widened and thus optimal for dialysis allografts. Subintimal pro-

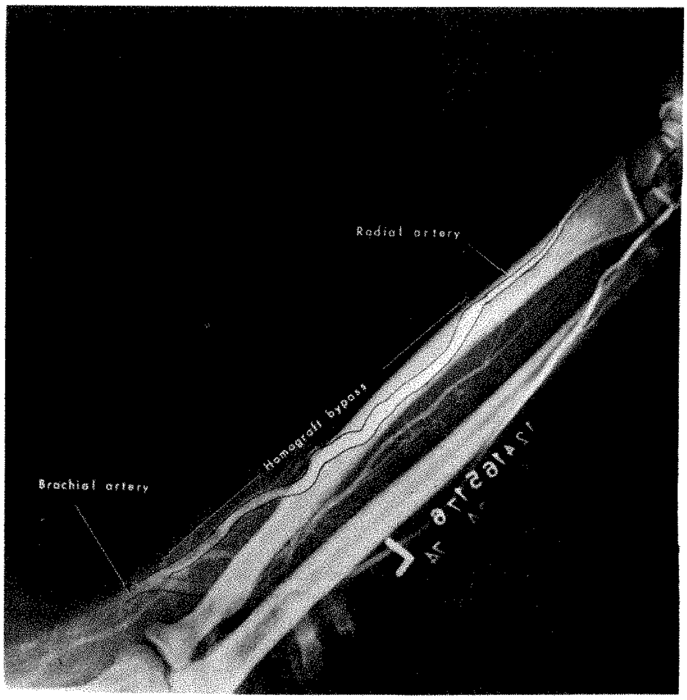


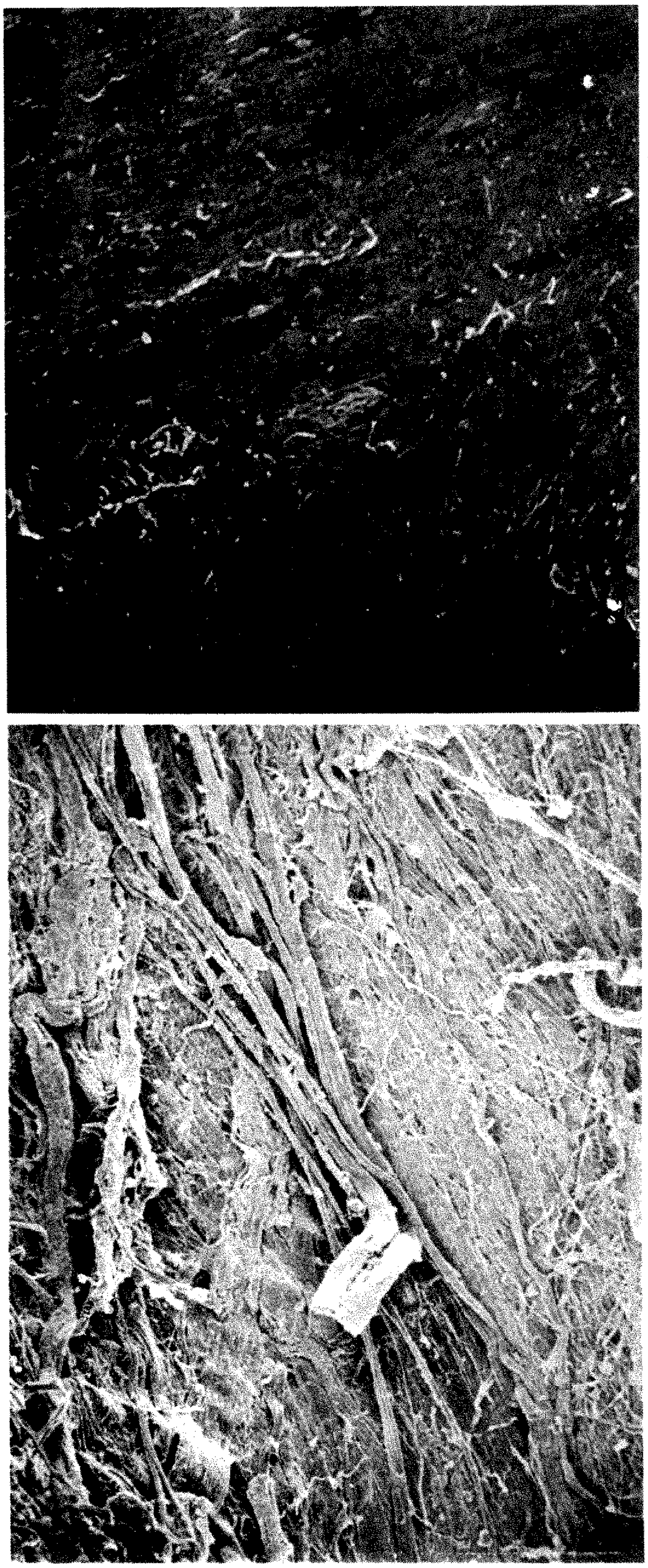
FIG. 5. Arteriogram demonstrates the vein allograft used for arterial-arterial bypass in patient with sickle cell disease.

liferative changes have not been observed to date in allografts used as A-V fistulas.

Renal transplantation was performed in one patient several months after placement of an allograft fistula with major blood group compatability between the vein donor and recipient. There was no evidence of accelerated rejection of the transplanted kidney.

The single allograft vein used as an arterial bypass from the brachial artery to the radial artery was performed in a patient with sickle cell disease. The arterio-arterial configuration (Fig. 5) was selected to avoid the distal ischemia or thrombosis of the palmar vasculature which might complicate a standard fistula in a patient with sickle cell disease. Hemodialysis was performed by removing blood from the bypass and returning blood into a peripheral vein. Application of topical thrombin on the puncture site was necessary to stop bleeding after the dialysis needle was removed. Subintimal thickening closed the graft at 6 months, and it was replaced with an allograft arteriovenous fistula which is functioning well at three months.

Scanning electron microscopy of the intimal surface of thawed allografts removed from patients with varicose veins who were not anticoagulated with heparin revealed a much rougher surface than the veins from patients with normal saphenous veins who received heparin and which were studied prior to freezing (Fig. 6). Scanning of varicose veins which were irrigated with a heparin-saline solution routinely showed rough surfaces.



FIGS. 6A and B. Scanning electron microscopy demonstrates marked difference in intimal surface of vein removed from patient treated with heparin systemically (top) and graft treated with simple irrigation of saline and heparin mixture (Bottom)

Discussion

Advanced arteriosclerosis, periarteritis, lupus erythematosis and other arterial diseases which often were responsible for the renal failure, together with constitutionally inadequate veins and veins obliterated by phlebosclerosis commonly impede the construction of autogenous arteriovenous fistulas. Depletion of conventional access sites by failure of A-V fistulas and repeated surgery to establish new fistulas continue to spur the development of more dependable access modalities. The appeal of the vein allografts lies in the fact that: 1) patients often have no suitable veins of their own; 2) only vein autografts have provided long term patency in small vessel surgery; and 3) problems have occurred with all of the alternate techniques for vascular access despite initial optimism.

Previous surgical experience with allograft vessels was not encouraging. Cadaver arterial allografts were tried as a substitute arterial conduit during the 1950's. About 50% of the grafts failed by the end of the fifth year because of thrombosis and aneurysm formation which appeared to follow histologically identifiable degenerative changes in the vessel wall.[10] The development of synthetic fiber grafts provided a readily available, dependable substitute which offered excellent long term results when applied to large vessels. However, synthetic grafts had a high rate of thrombosis when used below the inguinal ligament[8] and many patients had no saphenous vein to serve as an autograft. The persisting need for medium-to-small vessel bypass created new interest in vein allografts. After discovery of the immunologic rejection mechanism, another explanation for changes in the allograft walls became apparent. However, experimental studies with immunosuppressive agents did not demonstrate a lower incidence of thrombosis or a diminished intensity of rejection in vein allografts.[3] The low incidence of thrombosis and minimal histologic evidence of rejection in the main renal veins of transplanted kidneys is in stark[6] contrast and remains a puzzle. Ochsner[12] reported a high success rate bypassing femoral occlusions with fresh vein allografts in patients with the major blood group similar to that of the vein donor. Tice and associates successfully used frozen vein allografts for peripheral arterial replacement,[14] for coronary bypass grafts, and reported a single allograft used for an arteriovenous fistula.[15] The arteriovenous fistulas in this study were constructed from allograft veins of larger size (1.0-1.5 cm optimal diameter) than suggested by Tice[14] to facilitate dialysis.

Survival of allograft tissue after prolonged freezing seems unlikely. Microscopic examination of allograft veins after prolonged cold storage shows little change in smooth muscle and connective tissue.[14] However, cellular changes of necrosis would not be expected until some time after rewarming of the allograft by recipient blood flow. Rejection of the allograft or fibrous replacement of dead tissue could be expected from previous allograft experience,[3,12,13] although the vein allografts used in this study were used under significantly different conditions. After rewarming of the allograft, survival of any viable cells would be favored by the decreased immunologic response of the uremic patient and implantation of the graft in patients with major blood group compatability between donor and host.

The fast, low-pressure hemodynamic characteristics of arteriovenous shunts augur well for allograft patency. While frozen allografts used for subcutaneous arteriovenous dialysis shunts have not yet demonstrated long term patency superior to that of autogenous arteriovenous fistulas, the success of these grafts in patients with access problems is encouraging.

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Carotid Endarterectomy:

An Analysis of 234 Operative Cases

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This paper offers a computer-assisted analysis of the author's experience with 234 carotid endarterectomy procedures in 188 patients. The patients' ages, sex, smoking habits, symptoms, carotid bruits, arteriographic findings and associated diseases are summarized.

There were 28 operations in asymptomatic patients, 170 operations in patients with transient ischemic attacks (TIA), 35 operations in patients with a completed stroke and one operation in a patient with a stroke in evolution. After surgery, transient neurologic deficits were noted in both the asymptomatic group (two instances) and the group with TIA (5 instances); permanent neurologic deficits followed 4 operations in the TIA group (2.4% incidence). Two operative deaths occurred in the TIA group (1.2% mortality), and 10 deaths occurred after operation for a completed stroke (28.6% mortality). Nine of the deaths in the completed stroke group followed operations performed less than 2 weeks after a stroke.

A 100% followup was obtained, and the average period of followup was 48 months. Of the patients surviving operation, all in the asymptomatic group were judged functionally normal, 94% of the TIA group were either functionally normal or improved, 76% with a completed stroke were improved, and the patient with a stroke in evolution was unchanged. There were 69 late deaths with heart disease accounting for 58% of the deaths and stroke another 17%.

THE FIRST SUCCESSFUL carotid endarterectomy for stroke was performed by Dr. Michael E. DeBakey in 1953.[12] Since then, carotid endarterectomy has become the standard operative procedure for selected patients with cerebrovascular insufficiency caused by arteriosclerotic involvement of the proximal internal carotid artery. Numerous reports of clinical experience with carotid endarterectomy have demonstrated the efficacy of the procedure and have helped establish more precise indications for operation.[1-9,13] Nevertheless, there are still differences of opinion concerning various aspects of treatment. It is, therefore, important to evaluate periodically additional series of cases in an effort to resolve problems and further improve the results of surgical management. Accordingly, this paper reports a computer-assisted analysis of the author's experience with carotid endarterectomy during the 10-year period from 1963 to 1973; the results of this study are collated with those reported by other investigators.

Material and Methods

Between July, 1963, and July, 1973, a total of 234 carotid endarterectomies were performed for arteriosclerotic narrowing and ulcerated plaques in 188 patients. Forty-six patients underwent bilateral operations; in each patient, the procedures were done at least one week apart.

Operative cases were classified into four clinical categories designated as asymptomatic, transient ischemic attacks (TIA), completed stroke, and stroke in evolution. The classification of cases was based upon each patient's clinical findings and the relationship of these findings to the carotid artery subjected to endarterectomy. For example, a right carotid endarterectomy in a patient with a recent persistent neurologic deficit on the left side was classified in the completed stroke group; however, a left carotid endarterectomy performed later in the same patient without symptoms or signs referrable to the left carotid was classified in the asymptomatic group.

Carotid arteriograms were made in all patients prior to operation, but were not obtained routinely following endar-

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TABLE 1.

Arteriographic Findings	Appropriate Artery	Inappropriate Artery
Stenosis less than 50%	14	54
Stenosis less than 50% with ulcerated plaque	8	10
Stenosis 50% or greater	160	41
Stenosis 50% or greater with ulcerated plaque	40	11
Ulcerated plaque alone	4	6
Complete occlusion	8	23
Normal	0	50
No arteriogram	0	39

terectomy. The arteriographic examinations were performed under local anesthesia and sedation. In most patients, a percutaneous puncture technique was used for carotid arteriograms, and vertebral arteriograms were not made unless clinically warranted. The other patients underwent selective carotid arteriography as part of a 3 or 4 vessel catheter study performed by the transfemoral Seldinger technique. Hypaque 50% or Renografin-60 was manually injected and serial films were taken with an Elema-Schonander x-ray unit.

All operative procedures were performed under general endotracheal anesthesia. Hypercarbia was avoided, and an effort was made to maintain blood pressure near preoperative levels. Each patient was given 5,000 units of Heparin intravenously at least 5 minutes before occluding the carotid artery with vascular instruments. An internal shunt was used during all endarterectomies except those in which the internal carotid was completely occluded preoperatively. The arteriotomies were closed with continuous 6-0 Dacron sutures without the use of a patch. Heparin was counteracted with protamine sulfate only during the latter part of this series in those cases in which there had been significant hypertension or considerable bleeding from the wound surfaces. Postoperative anticoagulants were not used.

In evaluating the early results of surgery, deaths which occurred in the course of the operation, during the postoperative hospitalization period, or within 30 days after surgery were considered operative mortalities.

Followup examinations were made at regular intervals and at the conclusion of the study. If death occurred prior to the end of the study, the date and cause of death were ascertained along with the clinical condition of the patient prior to his demise. Late results of surgery were evaluated on the basis of a patient's functional status with respect to the artery subjected to operation. Each operative case was categorized as functionally normal, improved, the same, worse, or normal or improved then worse.

This series of operative cases was analyzed using the following method. Initially, a data extraction worksheet was designed to contain a numerical list of items which could be used to describe the salient features of each case. After reviewing a patient's records, items pertaining to that particular case were identified by circling the appropriate numbers on a separate worksheet; the worksheet was completed by assigning the case a series number and listing the patient's age and the followup period in months. Information recorded on the worksheets was keypunched on data cards, and a computer programed to read the cards and store the information on disc packs. Another program enabled the computer to analyze the stored information and provide specific answers in response to questions of interest.

Clinical Data

The 188 patients in this series included 118 males and 70 females; 178 patients were Caucasians and 10 were Negroes. The patients ranged in age from 32 to 89 with a median age by decade of 61 to 70 years. The average age for all patients was 64 years with males averaging 63 years and females 66 years.

Information regarding smoking was available in the records of 153 patients, and there were 91 smokers and 62 non-smokers. A non-smoker was defined as one who either had never smoked or had not smoked for at least two years.

There were 28 operations in asymptomatic patients, 170 operations in patients with TIA, 35 operations in patients with a completed stroke, and one operation in a patient with a stroke in evolution.

The 28 operative cases in the asymptomatic group were reviewed to determine the clinical condition which had prompted the decision for prophylactic surgery. The majority of operations (24) were performed in patients who had previously undergone endarterectomy on the opposite carotid because of either TIA or a completed stroke. Two operations preceded major surgical procedures for correction of concomitant arterial occlusive disease involving the lower extremities. The other two operations were done in patients hospitalized primarily for evaluation of asymptomatic carotid bruits.

A variety of symptoms attributed to cerebrovascular insufficiency were noted in the cases classified in the TIA and completed stroke groups. A complete list of symptoms comprised unilateral motor weakness, unilateral sensory deficit, amaurosis fugax, aphasia, dysarthria, dizziness, vertigo, syncope, diplopia, tinnitus, and photopsia. In a combined analysis of both groups of cases, the symptoms which occurred more frequently were dizziness (58%), unilateral motor weakness (41%), amaurosis fugax (26%), and aphasia and dysarthria (26%).

Preoperatively, a systolic bruit was audible over the appropriate carotid artery (i.e. the one subjected to operation) in 98 (42%) of the 234 operative cases. In 22 (9%) of the cases, a bruit was detected over the inappropriate artery only; 35 (15%) cases had a bruit over both carotid arteries.

Significant medical abnormalities other than cerebrovascular insufficiency were found in 210 (90%) of the

TABLE 2.

Clinical Group	Number of Deaths	Cause of Death	Procedure Mortality
Asymptomatic	0		0
TIA	2	Cardiac (1) Cerebral (1)	1.1%
Completed stroke	10	Cerebral (7) Cardiac (2) Pneumonia (1)	28.6%
Stroke in evolution	0		0

operative cases. The associated diseases and their incidence of occurrence were hypertension (51%), vascular disease affecting the lower extremities (44%), heart disease (44%), hyperlipidemia (25%), cerebral occlusive disease (22%), diabetes mellitus (18%), chronic bronchitis and pulmonary emphysema (15%), vertebral artery insufficiency (6%), and cerebral aneurysm (4%).

Arteriographic Findings

The preoperative arteriographic findings for both the appropriate and inappropriate arteries in all cases are summarized in Table 1.

Bilateral carotid arteriograms were made in 195 of the 234 operative cases. An analysis of the cases with unilateral arteriograms revealed that in 34 cases the secondary stage of a bilateral endarterectomy was performed without the benefit of repeat carotid arteriography. Also, unilateral arteriograms were obtained in three cases with a completed stroke who had undergone early operation (less than two weeks after onset of a stroke) and two cases in the TIA group. One of the TIA cases had a limited examination because a serious complication (acute thrombosis of the carotid with resultant amaurosis fugax) had developed during unilateral percutaneous carotid arteriography; fortunately, following emergency thromboendarterectomy with successful restoration of flow, there were no neurologic sequelae.

With regard to the findings in the appropriate carotid arteries, there were 14 cases with stenosis less than 50%, 8 cases with stenosis less than 50% and an ulcerated plaque, 160 cases with stenosis 50% or greater, 40 cases with stenosis 50% or greater and an ulcerated plaque, 8 cases with complete occlusion and 4 cases with an ulcerated plaque alone. Cases with stenosis less than 50% with or without an ulcerated plaque and cases with an ulcerated plaque alone were reviewed to determine their clinical category. Of the 14 cases with stenosis less than 50%, there was one in the asymptomatic group, 12 in the TIA group, and one in the completed stroke group. In the 8 cases with stenosis less than 50% and an ulcerated plaque, there were 2 in the asymptomatic group, 5 in the TIA group, and one in the completed stroke group. Three of the 4 cases with an ulcerated plaque alone were in the TIA group, and the other case was in the asymptomatic group. It should be noted that all of the cases in the asymptomatic group suffered a previous stroke caused by occlusive disease in the opposite carotid or cerebral arteries.

TABLE 3.

Time of Operation After Stroke	Number of Operative Cases	Postoperative Deaths
< 24 hours	8	3 (cerebral)
One to thirteen days	21	4 (cerebral) 2 (cardiac)
> 2 weeks	6	1 (carcinoma of lung and pneumonitis)

Vertebral arteriograms were made in 45 of the operative cases. The incidence of serious complications resulting from all arteriographic studies, whether involving one or more vessels, was 0.4% (1 in 234).

Early Results of Surgery

Seven operative cases required emergency reoperation because of postoperative hemorrhage. All of these cases had hypertension, and none received protamine sulfate following the use of Heparin. With the exception of one case, the hemorrhage occurred within one to 3 hours after endarterectomy. In 4 cases, there was excessive capillary bleeding from the skin and subcutaneous tissues alone. Two cases had bleeding from the arterial suture line, and in one case postoperative thrombosis of the internal carotid developed. The remaining case sustained a major hemorrhage from the carotid suture line 20 days after surgery; bleeding was thought to have been caused by defective suture material which had broken. Except for the postoperative death in the case with carotid thrombosis, the other cases recovered without ill effects.

After carotid endarterectomy, transient neurologic deficits were noted in both the asymptomatic group (2 instances) and the group with TIA (5 instances); permanent deficits followed 4 operations in the TIA group (2.4% incidence). When the asymptomatic and TIA groups were combined, the total incidence of transient and permanent neurologic deficits was 3.5% and 2% respectively. Although most (8 instances) of the neurologic deficits were noted within 24 hours after surgery, 3 instances of transient deficits developed later in the postoperative period (two on the third day and one on the tenth day). Some of the factors contributing to the development of postoperative neurologic deficits were operative hypotension, postoperative hypertension, the presence of cerebral and contralateral carotid occlusive disease, and the inadvertent compression of the operated carotid while elevating the mandible to prevent respiratory obstruction.

A total of 12 deaths occurred either during the postoperative hospitalization period or within 30 days after surgery;

TABLE 4. *Late Followup Analysis*

Number of Months	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	112	118	120	Total Number Cases	Average Months Followup
Asymptomatic	4	3	1	1	3	5	5	1	3				1		1							28	34
Transient Cerebral Ischemia	27	8	16	13	17	13	17	14	16	6	1	4	2	3	2	4	1	1	1	1	1	168	39
Completed Stroke	5		1		3	2	4	2	3	1	1	1		1				1				25	41
Stroke in Evolution													1									1	78

no deaths occurred in the course of the operative procedures. Table 2 outlines the procedure mortality for the various groups of cases. There were two deaths (one cardiac and one cerebral) in the TIA group, and the mortality rate was 1.2%. Ten deaths followed surgery for completed strokes (28.6% procedure mortality). In the completed stroke group, the causes of death were cerebral (7), cardiac (2) and pneumonia (1). There were no postoperative deaths in the asymptomatic and stroke in evolution groups.

The 35 cases in the completed stroke group were reviewed to determine the effect of timing of operation on procedure mortality. Results of this review are summarized in Table 3. Twenty-nine cases underwent endarterectomy less than 2 weeks after onset of a stroke; 9 of the 10 deaths in the completed stroke group followed surgery in these cases.

Eight operations in the completed stroke group were performed for complete occlusion of a carotid artery. Restoration of flow was possible in 6 cases; however, one case developed a carotid-cavernous sinus fistula following the use of a Fogarty embolectomy catheter to remove distal clot. Four deaths (3 cerebral and 1 cardiac) occurred postoperatively.

Twenty-three endarterectomies were done for carotid stenosis in the presence of a completely occluded carotid on the contralateral side. There were 4 operations in the asymptomatic group, 17 operations in the TIA group, and 2 operations in the completed stroke group. After surgery, a transient neurologic deficit was noted in one case (TIA). None of the cases developed a permanent neurologic deficit, and only one death (cardiac) occurred.

Late Followup

A 100% followup was obtained and the average period of followup was 48 months. Details of followup in terms of months and number of cases in each clinical group are depicted in Table 4.

The functional status of the surviving operative cases either at the completion of the study or prior to late death is shown in Table 5. All cases in the asymptomatic group were judged functionally normal, 94% of the cases in the TIA group were functionally normal or improved, 76% of the cases with a completed stroke were improved, and the case with the stroke in evolution was unchanged.

A total of 69 late deaths occurred during the followup period (Table 6). The majority of deaths (58%) were caused by heart disease; 17% of the deaths were attributed to stroke.

Discussion

It is generally agreed that arteriographic findings of either 50% stenosis or an ulcerated plaque constitute a significant surgical lesion in patients otherwise considered suitable candidates for carotid endarterectomy. Indeed, 212 of the

234 operative cases in this series had carotid arteriograms with such findings. It is noteworthy, however, that 14 of the remaining cases had arteriographic findings of stenosis less than 50% without obvious ulceration: in the absence of other etiologic factors, the area of stenosis was regarded as a probable source of platelet and atheromatous cerebral emboli.

Patients with carotid arteriosclerosis who are asymptomatic can be categorized as follows: 1) those with known stenosis or ulceration in one carotid after bilateral arteriograms and endarterectomy on the opposite side; 2) those with an asymptomatic carotid bruit who must undergo major surgery for other problems; and 3) those with an asymptomatic carotid bruit alone. The management of asymptomatic patients in all categories is a controversial issue.[2,10,11,12,14] In an important study concerned with this matter, Javid et al.[9] studied the natural history of carotid atheromas in 93 patients by means of serial arteriograms over a period of one to 9 years. They found a significant increase in size of the atheromas in 62% of the lesions studied. Also, Thompson[12] followed a group of 92 patients with asymptomatic carotid bruits who were not subjected to endarterectomy. During a 10-year followup period, 41 (45%) of these patients developed either TIA (26%) or completed strokes (19%). Additional studies are needed which allow for a comparison of the results of non-surgical and surgical treatment. At present, the author favors endarterectomy for asymptomatic patients with significant stenosis or ulceration who have undergone operation on the contralateral carotid. Asymptomatic patients with a carotid bruit who require other major surgery are first evaluated by arteriograms after which endarterectomy is performed if significant lesions are present. Although routine arteriography is not advised for patients with an asymptomatic carotid bruit alone, such patients who have arteriograms with significant findings are considered possible candiates for endarterectomy. The results of surgery for asymptomatic patients in this series (no postoperative deaths or permanent neurologic deficits) would seem to justify this approach.

In this series, a total of 198 carotid endarterectomies were performed in patients without a neurologic deficit prior to operation (asymptomatic and TIA groups). The operative mortality was 1%, and there was a 2% incidence of permanent neurologic deficits postoperatively. These results compare favorably with those reported by other investigators. Following 399 endarterectomies in which general anesthesia and a shunt were used, Thompson[12] noted a 0.25% operative mortality and a 1.5% incidence of permanent deficits. DeWeese et al.[4] performed 237 operations using general anesthesia and maintenance of normal or slightly hypertensive blood pressure without a shunt; they reported a mortality rate of 2%, and an incidence of permanent deficits of 9%. Fields et al.[5] reporting for the Joint Study of Extracranial Arterial Occlusion, reviewed 169 operations in which various methods were used to prevent operative cerebral ischemia; the operative mortality was 3.5%, and the incidence of permanent deficits was 7.7%.

TABLE 5.

	Asymptomatic	TIA	Completed Stroke	Stroke in Evolution
Functionally normal	28 (100%)	84 (51%)	1 (4%)	
Functionally improved		74 (45%)	19 (76%)	
Functionally same		3 (2%)	4 (16%)	1 (100%)
Functionally worse			1 (4%)	
Functionally normal or improved then worse		4 (2%)		

This study and others previously reported have shown that carotid endarterectomy performed less than two weeks after onset of a completed stroke is associated with a high operative mortality (up to 42%).[1,4,13] The risk of early surgery is primarily related to a change in the blood-brain barrier which permits increased vascular permeability after an acute persistent neurologic deficit; this change gradually resolves over a 6 to 12 week period. If blood flow is restored surgically during the first two weeks of the change in the blood-brain barrier, there is considerable danger of converting an ischemic infarct into a hemorrhagic one. Consequently, most surgeons now agree that patients should not be subjected to endarterectomy within two weeks of the development of a completed stroke. For similar reasons, operation is also no longer recommended for patients with a stroke in evolution.

It has become evident that the majority of patients with complete occlusion of the internal carotid fail to benefit from endarterectomy.[2] The mortality rate following operation for an acute occlusion is prohibitive, and the chance of restoring flow two or more weeks after occlusion is extremely low. As a result, many surgeons, including the author, believe that patients with this lesion should not be

TABLE 6.

Cause of Death	Asymptomatic	TIA	Completed Stroke	Stroke in Evolution
Cardiac	4	30	6	
Cerebral	2	9	1	
Malignancy	2	5	1	
Renal		1		
Pneumonia		1		
Pulmonary Embolism		2		
Following other surgery		2		
GI Hemorrhage		1		
Suicide		1	1	
Total Deaths	8	52	9	0

considered suitable candidates for endarterectomy. On the other hand, those patients with significant stenosis or ulceration in the opposite carotid should have surgical correction of the stenotic or ulcerated lesion. Twenty-three such procedures were performed in this series using general anesthesia, systemic heparinization, and a shunt for cerebral support; the operative mortality was 4.3% (one cardiac death), and there were no permanent neurologic deficits postoperatively.

Finally, the results of late followup in this series have substantiated the effectiveness of carotid endarterectomy in the prevention of recurrent stroke. The basic disease process of arteriosclerosis, however, remains unaltered, and there is no convincing evidence that endarterectomy prolongs survival. The majority of late deaths following endarterectomy have been caused by associated coronary arteriosclerosis.

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Congenital Duodenal Diaphragms in Adults:

A Delayed Cause of Intestinal Obstruction

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Congenital duodenal diaphragms in the adult are uncommon, unsuspected lesions that infrequently cause intestinal obstruction. The diaphragms may be single or multiple and are usually located near the ampulla of Vater. Three cases are summarized and the recent literature reviewed. At least 35 cases have been reported. Treatment most often consisted of duodenotomy, excision of the web and duodenal closure.

CONGENITAL DUODENAL DIAPHRAGMS are uncommon causes of intestinal obstruction, occurring once in every 9,000 to 40,000 births.[14] Although the lesion may be present in newborns, children, and adults, less than 40 of the reported 117 cases have been in adults.

Because of the delayed onset of symptoms, the lesion and diagnosis is often unsuspected in adults. Our recent experience with three cases has prompted this report and a review of the recent literature.

Case 1. A 73-year-old woman was admitted to The Cleveland Clinic Foundation Hospital in March 1974 with a two-month history of postprandial nausea and vomiting, abdominal discomfort, epigastric fullness, and a 9.1 kg (20 pounds) weight loss. She had been well until then, but thought that the inability to digest solid food precipitated this illness. Eye drops for glaucoma had been prescribed recently. There was no hematemesis, melena, or history suggestive of duodenal ulcer disease.

Physical examination revealed a thin, emaciated woman weighing 42.7 kg (94 pounds). The abdomen was soft, nontender, with a suggestion of fullness in the epigastric area. Laboratory values were all within normal limits. An upper gastrointestinal series showed a massively dilated stomach with no progression of barium beyond the duodenal bulb (Fig. 1). The diagnosis of duodenal obstruction, probably due to duodenal ulcer, was made and an operation advised. She refused surgery and left the hospital on a regimen of liquid diet, antacids, and instructions to eat smaller meals 6 times a day.

She returned to the Clinic two months later in May 1974 because of progressive symptoms and weight loss now 35 kg (77 pounds). Physical examination was unchanged. Her hemoglobin was 13.2 gm/100 ml, hematocrit value 39.9%, white blood count 8,600 mm^3 and urinalysis was normal. The serum sodium was 132 mEq/liter, chlorides 90 mEq/liter, CO_2 31 mEq/liter. An SMA-12 was within normal limits. The serum gastrin was 120 pg/ml. Gastric decompression was instituted via a nasogastric tube, and an operation was performed on May 8, 1974. A distended, hypertrophic stomach with a patulous pylorous was seen. There was no evidence of recent or past ulcer disease. An intrinsic thickening of duodenal mucosa was palpated in the descending duodenum proximal to the ampulla of Vater suggesting a diaphragm. A longitudinal duodenotomy was made, and two small apertures each 3 mm in diameter (Figs. 2 & 3) were noted in the diaphragm. The diaphragm was excised and the duodenum closed transversely in one layer.

The postoperative course was satisfactory, except for a transient mild psychoses which cleared in 72 hours. The patient was dismissed on the ninth postoperative day; a normal diet was advised. She was seen one month postoperatively and had gained 9.1 kg (20 pounds) during this time.

Case 2. A 60-year-old Caucasian woman was examined in October 1967. She had had recurrent epigastric pain and fullness since 1960. The pain, dull and aching, had increased in intensity during the previous two years, and was associated with nausea and vomiting. Physical examination revealed right upper quadrant tenderness. An upper gastrointestinal series showed a 2 cm narrowed segment in the descending duodenum.

On October 11, 1967, an operation was performed which revealed a duodenal obstruction. A duodenotomy was made, a membrane excised, and the duodenum was closed transversely in one layer. The postoperative course was satisfactory.

Case 3. A 59-year-old Caucasian man was examined in December 1969 because of severe episodes of vomiting for the past three years. He noted a tight feeling in the epigastrium that was brought on by eating. There was a 4.5 kg (10 pound) weight loss during the 6 months preceding admission. There was no hematemesis or melena.

Previous surgery included a right orchiectomy for seminoma in 1947, a bilateral mastectomy for gynecomastia in 1947, a transcolonic polypectomy in 1967, and a left renal artery endarterectomy and saphenous vein patch for renal vascular hypertension in 1968. The preoperative blood pressure was 140/100 mm Hg, and the postoperative blood pressure was 120/80 mm Hg without medication.

Results of laboratory testing including CBC, SMA-12, and electrolytes were normal. An upper gastrointestinal series revealed delayed

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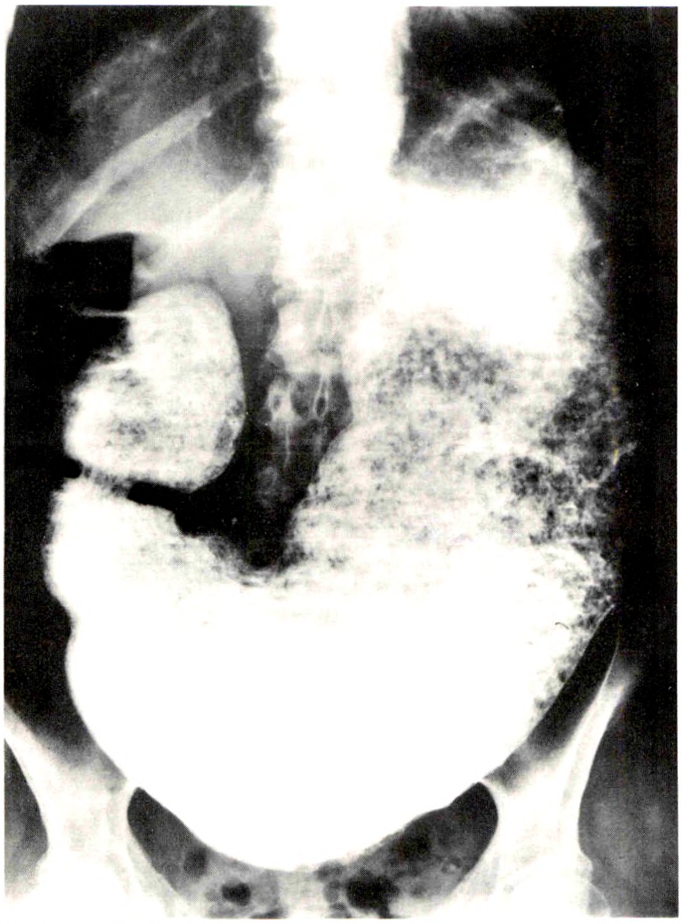

FIG. 1. A large dilated stomach and duodenal bulb. The narrowed area is seen distal to the bulb.

gastric emptying with evidence of significant retention at two and one-half hours. A gastroscopic examination on July 22, 1969, was normal. The patient was dismissed; small liquid feedings were advised, but he returned in December 1969 with continued fullness and weight loss. Because of continuing symptoms an operation was advised.

TABLE 1. *Results of Surgical Treatment: 35 Adult Patients with Duodenal Diaphragm*

Operation	No. of Patients	Results
None	10	(Autopsy Findings)
Gastroenterostomy (Alone)	2	1 cured; 1 died 5 days postop
Exploration	1	Diagnosis not made
Excision of Web	10	cured
Incision of web with or without duodenoplasty	1	cured
Miscellaneous*	11	

*Operations including vagotomy, gastrojejunostomy, Finney pyloroplasty, duodenoduodenostomy.

At surgery a congenital duodenal web, one inch proximal to the ampulla and obstructing the duodenum, was excised after a longitudinal duodenotomy was made. The duodenum was then closed transversely in one layer. The patient did well postoperatively and when seen one month postoperatively he had no abdominal complaints and had gained 1.4 kg (3 pounds).

Discussion

Duodenal diaphragms are uncommon lesions that infrequently cause partial or complete intestinal obstruction. Membranous obstruction accounts for only 0.8%-25% of all small intestinal obstructions and 2% of duodenal obstructions.

The cause of this lesion is thought to be one of several possible developmental defects, and the many theories offered reflect a lack of agreement on the etiology of this entity.

Bland-Sutton, in 1889,[18] believed that all intestinal stenosis or atresia occurred where tissues fuse or outgrowths occur. He explained duodenal diaphragms as a "developmental" accident that had happened in the region of the ampulla of Vater where a diverticula normally originates to form the liver and the pancreas.

A more popular theory was advanced by Tandler in 1900,[19] who studied the intestinal tract of embryos at 30

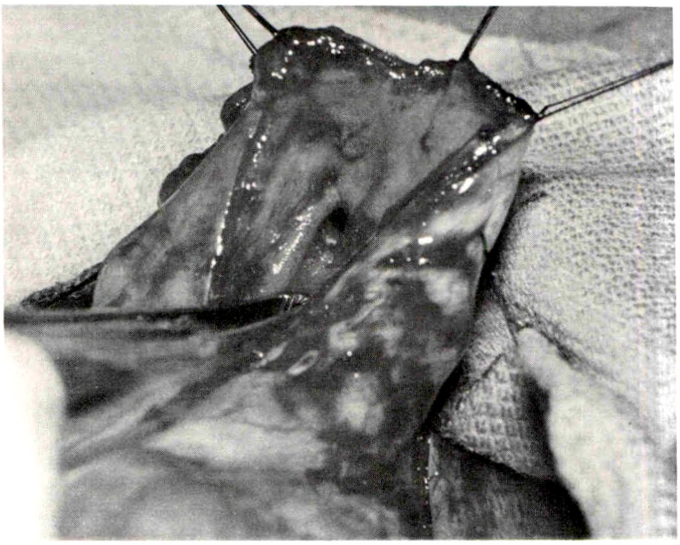

FIG. 2. The duodenum has been incised longitudinally. One aperture is easily visualized.

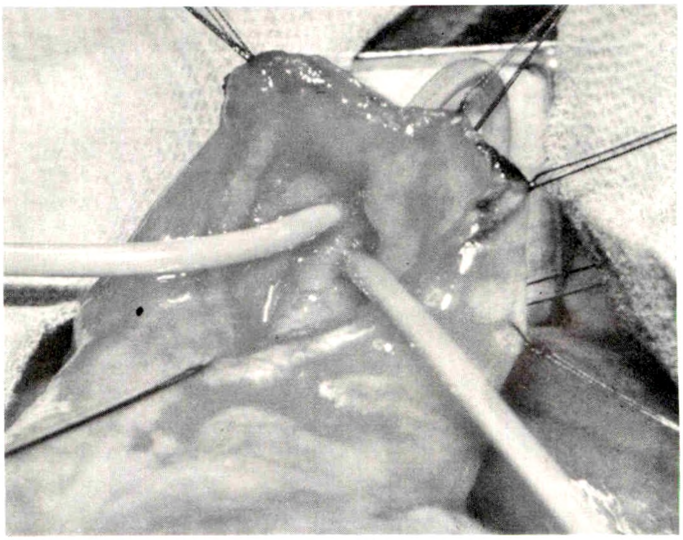

FIG. 3. A catheter has been placed through both lumens of the diaphragm.

TABLE 2. *Review of Literature*

Author	Date	Age, Sex	Symptoms	Operation	Time of Diagnosis	Relation of Web to Ampulla	Aperture	Results
Dorken & Evans[5]	1967	78, F	Vomiting, anorexia, weight loss	Duodeno-plasty	X-ray and Operation	Proximal	Not. spec.	Death
Barakat[2]	1970	36, M	Mid-epigastric pain, vomiting, weight loss	1st op web excised, duodenoplasty, vagotomy 2nd op. gastrojejunostomy	Operation	Proximal	10 mm	Cured
Raju[13]	1970	52, M	Cramping, abd. pain, vomiting	Web excised duodenoplasty · closure of gastrotomy	Operation	2nd part of duodenum	Not. spec.	Cured
Raju[13]	1970	52, M	Upper abd. pain, fullness in epigastrium	Web incised, Finney type pyloroplasty vagotomy	Operation	2nd part of duodenum	Small opening	Cured
Manhas[11]	1971	44, F	Nausea, vomiting, diarrhea, epigastric pain	2 webs excised gastroduodenostomy (Finney)	Operation	1 proximal other-distal	5 mm 3-4 mm	Cured
Bilton[3]	1971	46, F	"Hunger pain"	Web excised duodenoplasty	Operation	Proximal	2-3 mm	Cured
Bilton[3]	1971	61, M	Abd. pain, vomiting, anorexia, weight loss	Web excised gastrojejunostomy, vagotomy	Operation	Proximal	2 mm	Cured
Reismann & Deutsch[15]	1971	34, F	Vomiting, malaise	Duodeno-duodenostomy	Operation	? near ampulla	5mm	Cured
Ahmed et al.[1]	1972	54, M	Upper abd. fullness eructation	2 webs excised	Duodenoscopy	Both proximal	4 mm and 7 mm	Cured
Mackey et al.[9]	1974	72, F	Abd. pain, vomiting, bloating	Web excised gastro-duodenostomy	Operation	Proximal	5 mm	Cured
Cooperman, Adachi, Rankin, & Sivak	1974	74, F	Post-prandial nausea and vomiting	Web excised duodeno-plasty	Operation	Proximal	2 mm 3 mm	Cured
	1974	61, F	Epigastric pain-fullness	Web excised duodenoplasty	Operation	Proximal	Not. spec.	Cured
	1974	59, M	Vomiting, epigastric fullness	Web excised duodenoplasty	Operation	Proximal	Not. spec.	Cured

to 60 days of development. He observed that during this time the entire intestinal lumen became occluded by proliferating epithelium and a solid core formed. A stage of vacuolization then occurred so that cystic spaces developed into establishing a patent intestinal lumen. Incomplete vacuolization then led to the development of a diaphragm.

Boyden et al.[16] extended this work to explain why the stenosis takes place near the ampullary region. They noted that the ampullary region is normally the narrowest in the duodenum. Studying embryos at various stages of development, they observed that as vacuoles coalesce, openings from the pancreatic and biliary ducts join the future epithelial lining at the ampullary level. Any delay in vacuolization here will then lead to stenosis in an already narrowed segment.

Saunders and Lindner[16] believe that the duodenum develops in four stages. Problems in the third stage would lead to atresia, stenosis, or diaphragm formation, depending on the degree of abnormal development. Vascular accidents in utero, particularly ones that interfere with mesenteric blood supply, have been responsible for narrow, stenotic, or atretic intestinal segments.[8] Over one-half of the reported cases occur in newborns or within the first year of life. An associated increased incidence of mongolism[10] and esophageal atresia[14] has been reported with congenital duodenal obstruction.

The severity of the symptoms varies, and may depend on the size of the opening in the diaphragm and the age of the individual at the onset of symptoms. That some lesions are minimally symptomatic or overlooked is attested to by the fact that 10 cases have been discovered at autopsy alone, and at least one has been missed at laparotomy. Since well over half of the reported cases have occurred in newborns within the first year of life, these must reflect nearly complete duodenal obstruction.

If the diaphragm is incomplete and only partially obstructs the duodenal lumen, the onset of symptoms may be delayed for years, and obstructive symptoms will be only minimal and intermittent. Krieg[11] has stated that the onset of symptoms in 30% of the patients is after age 24. The supposition that a direct relationship exists between onset of symptoms and size of apertures with large openings having a later onset of symptoms, is only that and it is difficult to understand why patients who have very small openings may maintain satisfactory nutrition for so many years. This was clearly evident in our first case in which two 3 mm openings were asymptomatic for 72 years!

Histologic examination of the membrane reveals thickened mucosa and submucosa and normal muscle layers.[17] The openings in the diaphragm vary from 2.0 to 10 mm and are more often single than multiple. In 75% of cases, the diaphragm is located near the ampulla,[2] and the opening is usually eccentric rather than central.

The diagnosis is most often made by upper gastrointestinal series which reveals a dilated duodenal bulb and stomach proximal to the web without evidence of pyloric ulceration. More recently, endoscopy has helped in the diagnosis of at least one reported case.[1]

The more recent complete review of duodenal diaphragms in the adult was published in 1967 by Smiley, Perry, and McClelland who collected 22 reported cases.[17]

Since then we have found 13 others including the three we are presently reporting (Table 1). The symptoms were similar in nearly all cases and consisted of epigastric fullness, nausea, vomiting, and weight loss. The age range was from 36 to 78 years, with at least two patients in their eighth decade at the time the diagnosis was made. Ideally, the treatment is surgical, although traumatic rupture or cauterization via an endoscope may be feasible in the future.

A direct surgical approach to this problem was suggested by Morton in 1922[12] who proposed excision of the diaphragm via a duodenotomy. This approach was suggested after autopsy examination of one case. He was able to perform one such operation in 1923.[19] The first successful operation for a duodenal diaphragm in an adult, a 32-year-old woman, was reported by Kreig[7] in 1936.

Because of the relatively few cases of duodenal diaphragm reported in adults, surgical treatment has varied and several operations have been suggested. These have included gastrojejunostomy, side-to-side duodenojejunostomy, and duodenotomy with excision of the diaphragm, and then longitudinal or transverse duodenal closure. A summary of 35 operations for duodenal diaphragm in adults is shown on Table 2. These include 22 cases summarized by Smiley, Perry, and McClelland,[9] 10 cases summarized, and the 3 cases we have reported. Although several operations have yielded good results, the simplest and most direct approach would favor duodenotomy and excision of the diaphragm. This operation performed in 11 patients yielded excellent results in 10 patients, and the same operation with transverse closure of the duodenotomy was done in our 3 cases.

The entity of duodenal diaphragm should be kept in mind in every adult with a history or findings of an "atypical" duodenal ulcer with obstruction, particularly when no ulcer is found at surgery.

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Pancreaticoduodenal Preservation by Hypothermic Pulsatile Perfusion for Twenty-four Hours

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Pancreaticoduodenal grafts remained viable after transplantation only if a modified plasma perfusate with high osmolarity was used during the 24 hours of preservation. When regular plasma perfusate was used during the pancreaticoduodenal preservation, irreversible damage resulted, and all dogs died of ischemic or vascular changes in the first few days after transplantation.

IDEZUKI, GOETZ, AND LILLEHEI[10,12,13] were the first to successfully preserve pancreaticoduodenal grafts by using 24 hours of hypothermia and hyperbaria. Since then isolated reports.[2–5,22,27] indicate that pancreas preservation is feasible for short periods of time, although the current kidney preservation technique has not always been successful for the pancreas. In this report we analyze the effect of current hypothermic pulsatile perfusion techniques, for 24 hours, on transplanted pancreaticoduodenal grafts.

Materials and Methods

Twenty-five adult mongrel dogs weighing between 15 and 25 kg were used as donors of pancreaticoduodenal segments. After fasting for one day, the dogs were anesthetized with sodium methohexital for induction and halothane for maintenance. The pancreas and the first and second portions of the duodenum were resected with the celiac trunk and the portal vein as the vascular pedicle (Fig. 1). The pancreaticoduodenal grafts were washed out through the celiac trunk with a cold (4C) Ringer's lactate solution (300 ml) containing heparin (10,000 u/l) and procaine (1 gm/l). The proximal end of the duodenum was closed as a blind end, and a catheter was inserted into the distal end to collect the pancreaticoduodenal juice during perfusion. The pancreaticoduodenal segments were preserved by hypothermic pulsatile perfusion (6C, pH 7.4-7.6, Po_2 2l/min, Pco_2 30 ml/min, pulse rate 60/min) with variable perfusate systolic pressures (5-30 mm Hg) in the Mox 100 system (Waters Instruments Inc.) (Fig. 2). Two perfusate solutions were used. The first perfusate was cryoprecipitated pooled canine plasma (CPP) containing 200 ml/l of distilled water, 2 gm/l of methylprednisolone, 170 units/l of regular insulin, 1,000,000 units of penicillin, 8 ml/l of $MgSO_4$ 20%, and 2.5 ml/l of KCI 10%. The osmolarity was adjusted to 260-280 mOs/l, with 25% mannitol (30-50 ml), the pH to 7.4-7.6, and the electrolytes were maintained at an extracellular concentration. The second perfusate was cryoprecipitated plasma modified (MCPP) by the addition of 200 ml/l of human albumin (Cutter Lab) and 5-7 gm/l of dextrose. No mannitol was added to this solution. The osmolarity was adjusted to 300-310 mOs/l, the pH to 7.4-7.6 and the electrolytes were maintained at an extracellular level.

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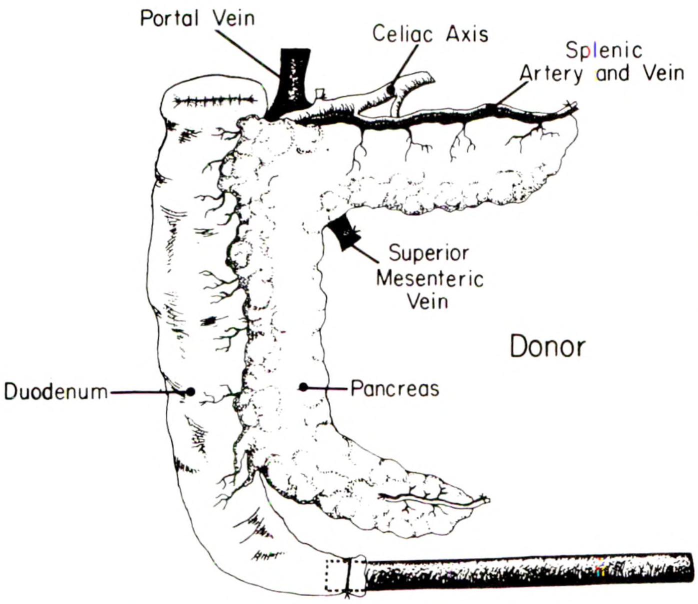

FIG. 1. Schema of pancreaticoduodenal graft prepared for preservation and transplantation.

During perfusion, perfusate pressure, flow rate, pH, P_{CO_2}, lactic dehydrogenase (LDH), glutamic oxalacetic transaminase (SGOT), lactic acid, and osmolarity levels were recorded at 0, 2, 6, and 24 hours. The pancreaticoduodenal juice was collected at 2, 6, and 24 hours for determination of amylase, trypsin, and bicarbonate levels. After preservation the pancreaticoduodenal allografts were placed in the right groin of unrelated recipient dogs. The vascular anastomosis was performed between the recipient's superficial femoral artery and vein, and the donor's celiac axis and portal vein (Fig. 3), External duodenal fistula was created by using a duodenal (Wangensteen) cannula. A total pancreatectomy was performed in the recipient dog immediately prior to the transplantation procedure and biopsies of the pancreas graft and duodenum were taken immediately after transplantation.

Daily intravenous administration of Ringer's lactate solution with 5% dextrose (1 l), calcium gluconate (10 ml/l), sodium bicarbonate (10-20 mEq/l) and ampicillin (l gm/l) was given for 5 days to maintain body fluids. Oral feeding was begun by the second postoperative day and 2600 mg of oral pancreatin was given daily. All recipients were immunosuppressed with 5 mg/kg/day of azathioprine and 2 mg/kg/day of prednisone. The endocrine and exocrine functions were evaluated daily by fasting blood sugar levels of blood amylase determinations. Pancreaticoduodenal juice was collected each day and amylase, trypsine and bicarbonate levels were recorded.

Twenty-five recipient dogs were divided equally into 5 groups, according to the type of perfusate and perfusate pressure used: Group I—control, fresh transplant without perfusion; group II—pancreaticoduodenal graft perfused with CPP at a pressure of 5 mm Hg for 24 hours; group III—similar to group II with a perfusate pressure of 10 mm Hg; group IV—similar to groups II and III with a perfusate pressure of 25 mmHg; and group V—pancreaticoduodenal graft perfused with MCPP at a perfusate pressure of 25 mmHg for 24 hours.

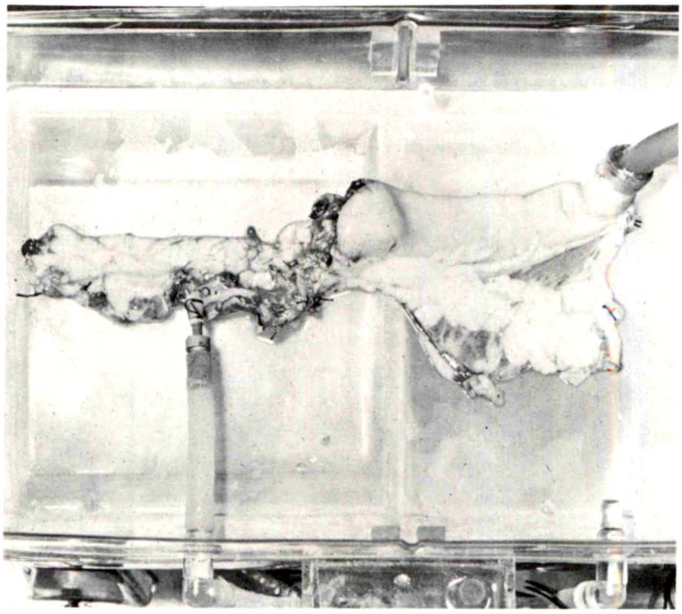

FIG. 2. Pancreaticoduodenal graft after 24 hours hypothermic pulsatile perfusion with MCPP at 6 C on the Mox 100 perfusion-preservation apparatus (Waters Instruments Inc.).

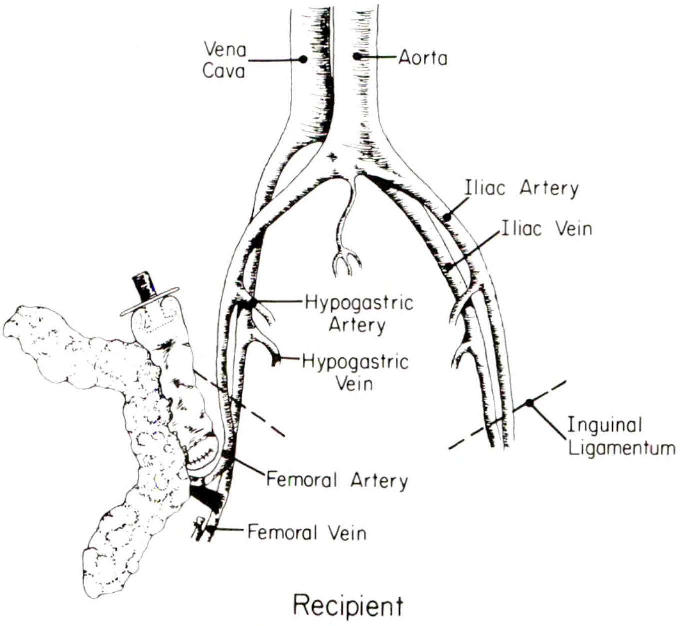

FIG. 3. After transplantation, the donor pancreaticoduodenal graft lies in the recipient groin. The vascular supply is established by anastomosing the celiac axis to femoral artery end-to-end, and the portal vein to femoral vein end-to-side.

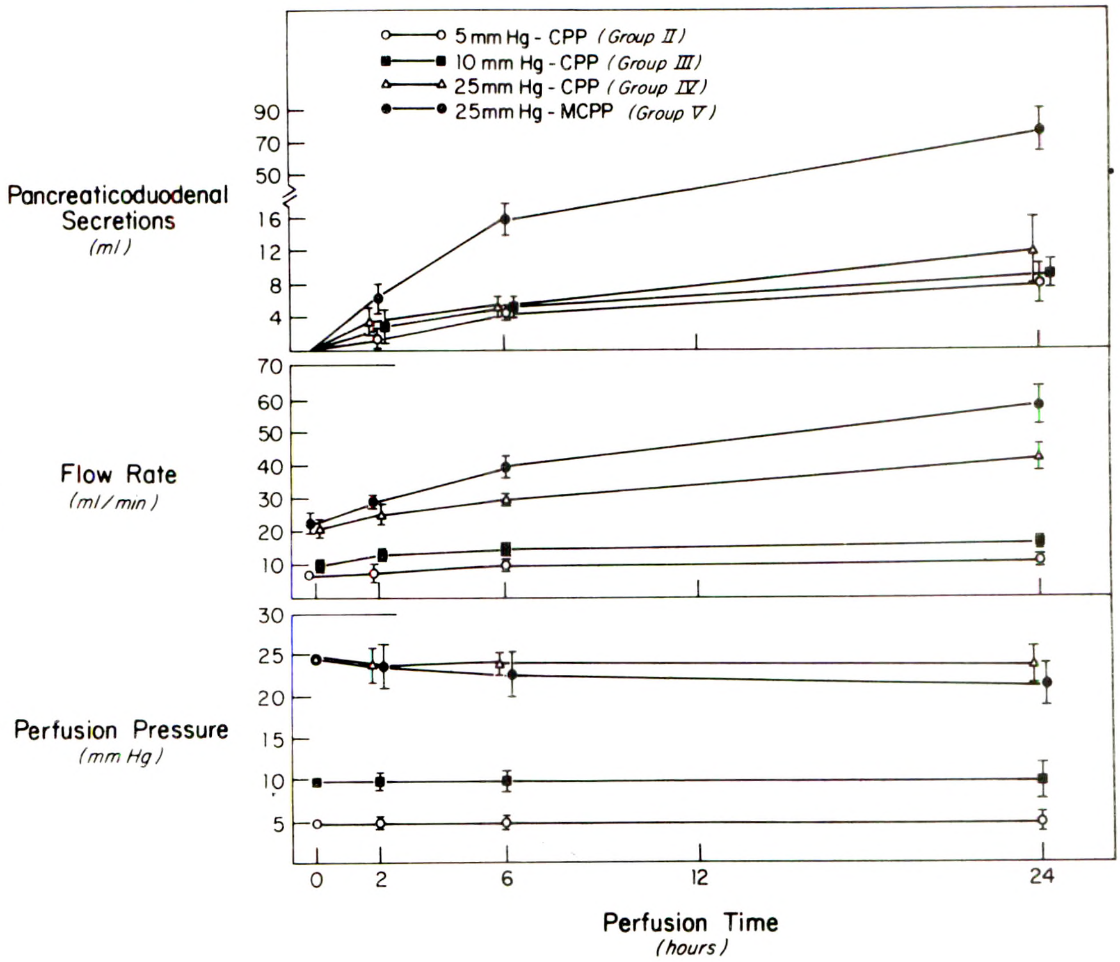

FIG. 4. Changes in perfusion pressure, flow rate, and pancreaticoduodenal secretions during 24 hours of hypothermic pulsatile perfusion of pancreaticoduodenal grafts.

Results

Perfusion changes: Figure 4 compares the perfusion pressure, flow rate, and pancreaticoduodenal secretions measured during the preservation of all segments. Group IV and V dogs had a progressive decrease in vascular resistance and an increase in perfusate flow rate. Group II and III animals had no improvement in flow rate, and their vascular resistance consistently increased. There were no significant changes in perfusate pressure in either of these four groups. Animals in groups II, III, and IV (CPP at 5,10,25 mm Hg) gained more than 30% of their original weight in 24 hours; while group V dogs (MCPP at 25 mm MHg) gained only a little weight. There was a minimal amount of pancreaticoduodenal secretion in the first three groups (II,III,IV) of perfused segments, but in the last group (V) the secretions significantly increased (P=0.001) after the first hours of perfusion. There was no duodenal peristalsis observed in any of the perfused pancreaticoduodenal grafts.

Fig. 5 illustrates the changes in bicarbonate, trypsin, amylase and pancreaticoduodenal secretions during perfusion. Group V animals had the best excretory capacity. The flow, amylase and trypsin changes were significantly higher (P=0.001) in the MCCP perfusate group (V) at 25

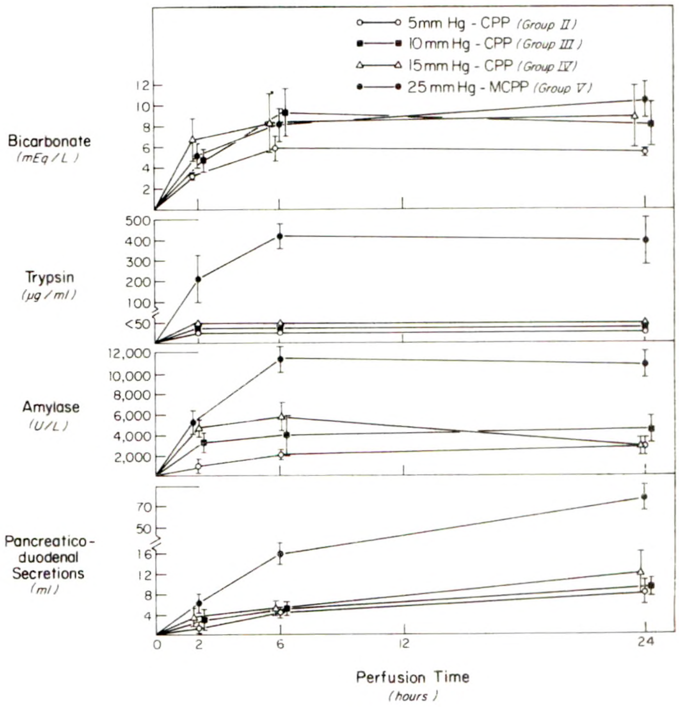

FIG. 5. Bicarbonate, trypsin, amylase and pancreaticoduodenal sercretion changes during 24 hours of hypothermic pulsatile perfusion.

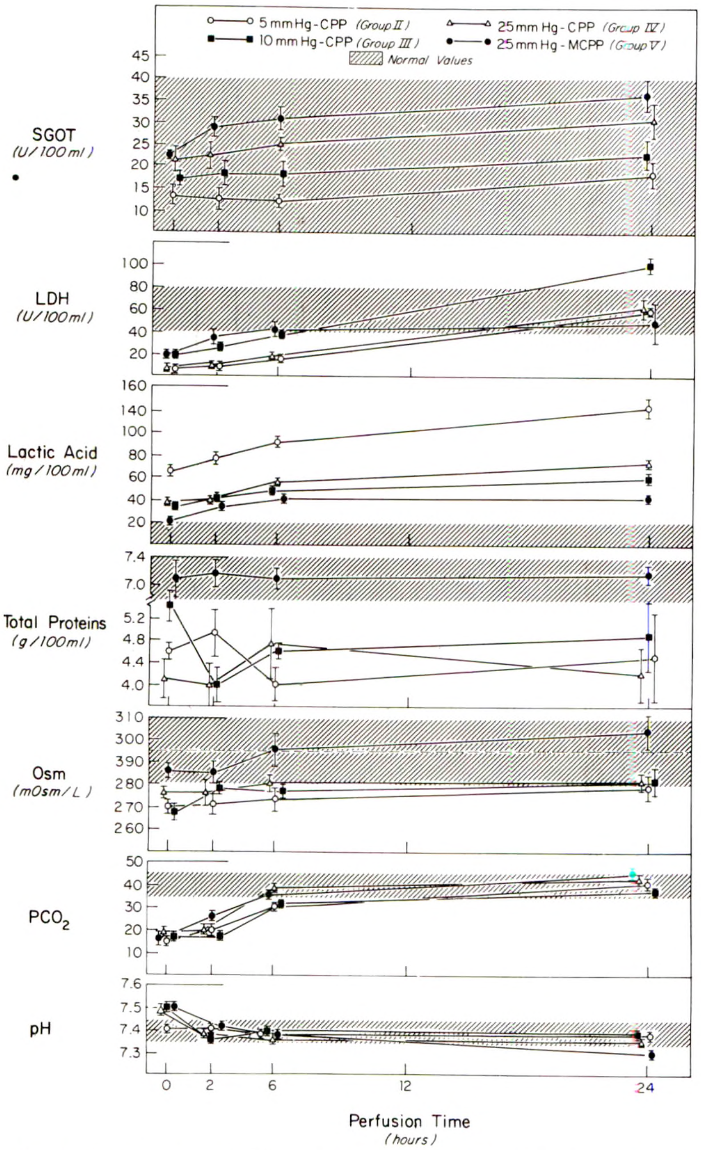

FIG. 6. Chemical, metabolic, and enzymatic changes during 24 hours of hypothermic pulsatile perfusion of the pancreaticoduodenal graft (shaded areas represent normal range).

mm Hg than the CPP groups (II,III,IV) at lower perfusion pressures. The bicarbonate activity was also higher in group V animals but it was not significant (P=0.5).

Fig. 6 shows the changes in pH, PCO_2 osmolarity, total proteins, lactic acid, LDH and SGOT during perfusion; the shaded areas represent their normal values. There were no significant differences in pH and PCO_2 in all four groups. The osmolarity and total proteins were moderately increased for group V from the beginning of perfusion; the other groups had lower values throughout perfusion. The lactic acid levels in groups II, III, IV were considerably higher than in group V. The SGOT levels were normal in all groups. The LDH level of group III was above normal.

Immediately after revascularization the pancreaticoduodenal grafts in groups, II, III, and IV animals showed edema, hemorrhage, and venous congestion, but no duodenal peristalsis. The grafts in group V had minimal edema and duodenal peristalsis. The secretions of these grafts were initially hemorrhagic but they became clear one to two hours after transplantation. There were no further signs of bleeding, but there were occasional signs of venous congestion.

Recipients of fresh pancreaticoduodenal segments survived a mean of 14.6 days (Table 1). Table 2 shows that 24 hours of hypothermic pulsatile perfusion with CPP at a perfusion pressure of either 5, 10, or 25 mm Hg significantly decreased graft survival. The recipients of pancreaticoduodenal grafts perfused with MCPP at 25 mm Hg, survived longer than even the fresh control grafts.

Fig. 7 compares the blood glucose, serum amylase and white blood cell values of fresh pancreaticoduodenal segments (group I) after transplantation with grafts that had received pretransplant perfusion with MCPP at 25 mm Hg (group V), and survived an average of about 3 weeks (one dog survived 6 weeks).

Also, the flow, amylase, trypsin, and bicarbonate levels in the pancreaticoduodenal juice of the fresh grafts and of the MCPP grafts are compared in Fig. 8. There are no significant posttransplant differences between these two groups of pancreaticoduodenal grafts (Fig. 7 and 8). The other groups of perfused segments were unsuitable for comparison because of their short posttransplant survival.

Posttransplant hemorrhagic necrosis and interstitial edema occurred frequently in the other three groups of animals (II,III, and IV). The only abnormal histologic characteristics we could find was minimal interlobular edema in the long-term survivors (I and V), although there was evidence of other changes compatible with rejection. The duodenum of two of these dogs showed mononuclear cellular infiltrate (particularly in the submucosa), early thickening of all layers, and signs of

TABLE 1. *Causes of Recipient Death After Pancreaticoduodenal Preservation and Allotransplantation*

Time of Death	Cause of Death	Groups I*	II	III	IV	V
1 to 5 days	Early vascular thrombosis		2	2	2	0
	Generalized sepsis		1	0	0	0
	Intussusception		0	1	0	0
	Pneumonia		0	1	1	0
	Hemorrhagic pancreatitis		1	1	2	0
	Ischemic necrotic pancreas duodenum		1	0	0	0
5 to 40 days	Late vascular thrombosis	0	0	0	0	1
	Duodenum perforation	1	0	0	0	1
	Duodenum rejection	1	0	0	0	1
	Pancreas rejection	1	0	0	0	0
	Cachexia	2	0	0	0	2

*Group I—fresh pancreaticoduodenal graft.

TABLE 2. *Pancreaticoduodenal Allograft Survival (Mean Values ± S.D.)*

Groups	Days	Significance† (p values)
I. Control	14.6 ± 3.0	———
II. CPP 5 mmHg*	4.5 ± 1.1	<0.01
III. CPP 10 mmHg*	3.8 ± 1.5	<0.01
IV. CPP 25 mmHg*	4.7 ± 1.4	<0.05
V. MCPP 25 mmHg*	18.3 ± 4.5	=0.5

*All these groups had 24 hr. of hypothermic pulsatile perfusion.
†All P values are compared to those of the control group.

hemorrhagic necrosis. The pancreas of another dog showed induration, atrophy, and diffuse interstitial fibrosis.

Discussion

A modified plasma perfusate (MCPP) with higher concentrations of protein and osmolarity, at 25 mm Hg of perfusate pressure, maintains the viability of pancreaticoduodenal allografts perfused for 24 hours. When we used a regular plasma perfusate (CPP) at the same perfusion pressure, the survival of the pancreaticoduodenal allografts decreased significantly. Lowering the perfusate pressure in an attempt to decrease the formation of edema did not improve the survival results.

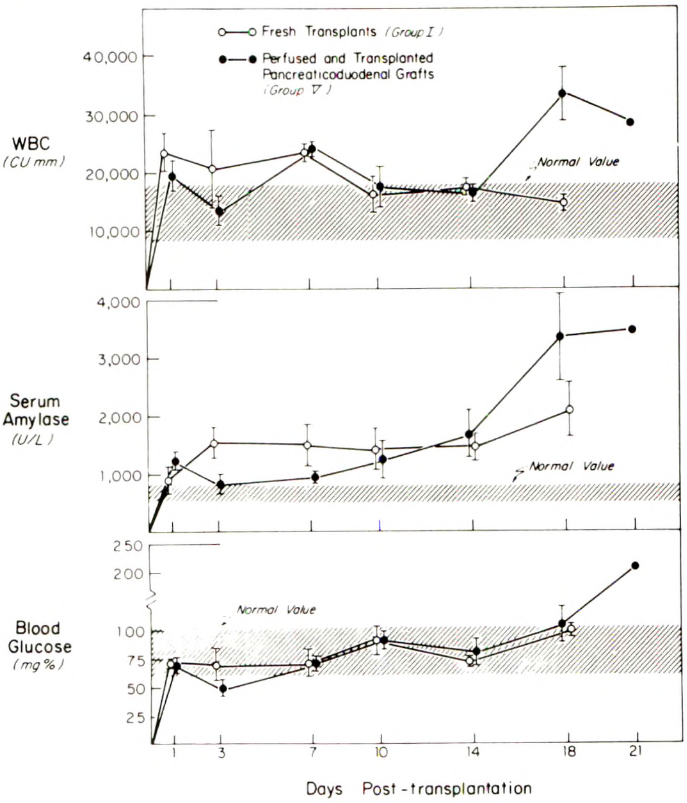

FIG. 7. Blood glucose, serum amylase and WBC values in fresh pancreaticoduodenal allografts (group I) and perfused and transplanted pancreaticoduodenal grafts (group V) (shaded areas represent normal range).

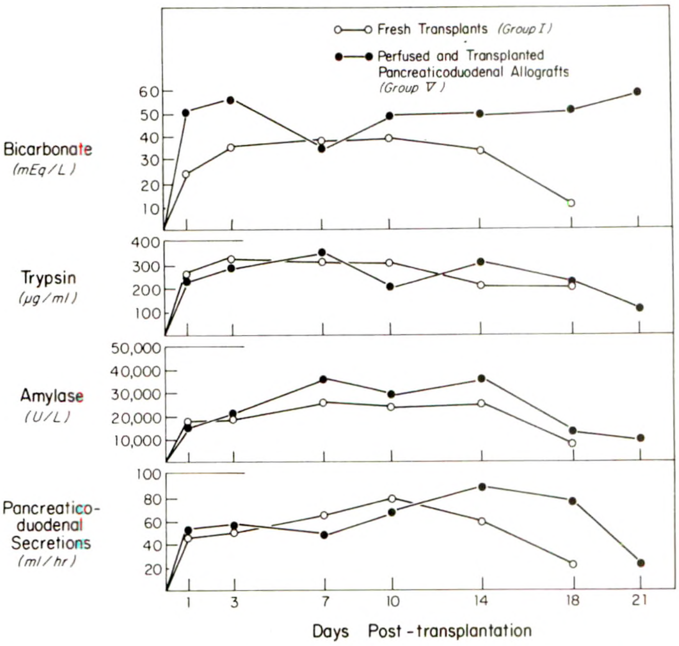

FIG. 8. Pancreaticoduodenal secretions, amylase, trypsin and bicarbonate in the pancreaticoduodenal juice of fresh and preserved pancreaticoduodenal allografts.

It is not clear how a modified plasma perfusate acts to improve *in vitro* function and posttransplant survival. The high protein content, formed mainly by albumin, increases the colloid osmotic pressure of the plasma. Consequently, the colloid osmotic pressure in the capillaries overbalances the relationship with the mean hydrostatic pressure, which increases the tendency of fluid to leave the tissue spaces and to enter the capillaries. As a result, fluid does not collect in the tissue spaces, the tissue pressure therefore decreases, edema does not result, and a better circulatory dynamic is established.[21] As a result, pancreaticoduodenal allografts perfused for 24 hours have a better *in vitro* function. Using a similar principle, Toledo-Pereyra and associates[25] perfused canine livers and lungs with a modified plasma perfusate. They found that organs perfused with the plasma perfusate that has a high osmolarity and high protein content had better *in vitro* function. In addition, albumin prevented the formation of pulmonary edema by increasing the colloid osmotic pressure and favoring the movement of fluid from the extracellular and interstitial spaces to the intravascular compartment.[26]

Our best results were achieved with MCPP at 25 mm Hg perfusate pressure. Although we have not studied the effect of high perfusate pressure on these segments, we believe that higher pressures will irreversibly damage the preserved pancreas. Additional studies will clarify this problem and determine the ideal perfusate pressure for pancreas preservation. In general, only indirect evidence indicates the pancreas requires a lower perfusate pressure than that used for kidney perfusion (60 mm Hg).

Methylprednisolone is a component of our modified plasma perfusate because we believe it plays an important role in preservation of pancreaticoduodenal segments; however, we did not include a control group of modified plasma perfusate without methylprednisolone.

The exocrine and endocrine function of the pancreas during preservation and immediately after transplantation has been studied extensively.[6,7,14,16,17,19,20,24] In addition, the response of the exocrine function of the pancreas to different drugs such as amphotericin B, secretin, and gastrin has also been studied.[9,18,28] In general, our results also indicate that a well-preserved pancreaticoduodenal segment will have high flow, minimal edema and weight gain, stable perfusate pressure, minimal increase of lysosomal enzymes in the perfusate fluid, and increased volume and metabolites of the pancreaticoduodenal juice. Idezuki[1,8,11,15,23] observed that insulin production in response to glucose stimulation appeared to be the most sensitive test of the functional viability of the preserved pancreatic grafts. We did not study the insulin response to a glucose load. We indirectly determined the endocrine capacity of the pancreas by the ability of the pancreaticoduodenal segments to maintain a previously pancreatectomized dog.

Twenty-four hours of pancreaticoduodenal preservation causes irreversible damage when a regular cryoprecipitated plasma is used as a perfusate. If a modified plasma perfusate is used there are long-term survivors, the pancreaticoduodenal segments are viable, and the early vascular changes and necrosis are avoided.

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Presence of Endothelium in an Axillary-femoral Graft of Knitted Dacron With an External Velour Surface

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An axillary-bilateral common femoral graft of knitted Dacron with an external velour surface was examined within one hour after the patient's death from non-graft-related causes. The prothesis, implanted for 20 months, was patent and was completely healed over 32% of the flow surface—that is, full wall fibrous tissue encapsulation of the graft had occurred, and 32% of the flow surface was endothelialized. The remaining flow surface was formed of fibrin, but fibrous tissue healing had reached the inner surface of the graft material, and the fibrin overlay was very thin. The healed portions of the graft included not only the areas adjacent to the anastomoses, but were scattered throughout the 45 cm length of the prosthesis. To our knowledge, this is the first report of complete healing (fibrous tissue encapsulation and endothelialization) documented at points beyond the pannus ingrowth at the prosthesis-artery anastomosis.

TO OUR KNOWLEDGE, complete healing (see Fig. 1) of conventional, relatively smooth-walled porous fabric vascular prostheses has not been demonstrated in man except within a few millimeters of each suture line.[1,7] Here it develops by transinterstices ingrowth from the perigraft tissues and by pannus extension across the suture line from the host artery. Our specimens indicate that pannus ingrowth extends only about 6-10 mm in man. Between these limited areas adjacent to each suture line, the inner surface of conventional porous prostheses has consistently been covered with compacted fibrin. The specimens studied have all been recovered from patients who died of nongraft causes, and all were patent at time of death.[1,7]

Previously, we reported[5] the presence of what was probably complete healing at 182 days (6 months) in a man having a non-crimped external velour knitted Dacron aorto-bilateral common femoral bypass graft. The word "probably" is used here, because, while other criteria for complete healing were present, endothelium could not be demonstrated on the luminal surface. However, endothelium is very delicate, and it must be stained almost immediately in order to be identified. In this case, several hours had elapsed between the time of death and silver staining of the specimen.

In this paper, we report the presence of islands of endothelium scattered throughout another graft of the same type—knitted Dacron with an external velour surface—but with a random crimp configuration. This graft, a left axillary-bilateral common femoral artery bypass graft, was removed upon death of the patient 20 months postoperatively. Islands of complete healing were found scattered throughout the 45 cm long prosthesis. Thirty-two per cent of the flow surface was covered by endothelium, and the remainder by compacted fibrin.

Although complete healing was attained in only about one-third of the area of the graft, to our knowledge this is the first description of such healing in man at sites far removed from the limited areas of pannus ingrowth adjacent to the anastomoses to the host artery. In 1964, DeBakey and colleagues reported endothelium on fibrin in a graft which had been in a patient for almost 4 years.

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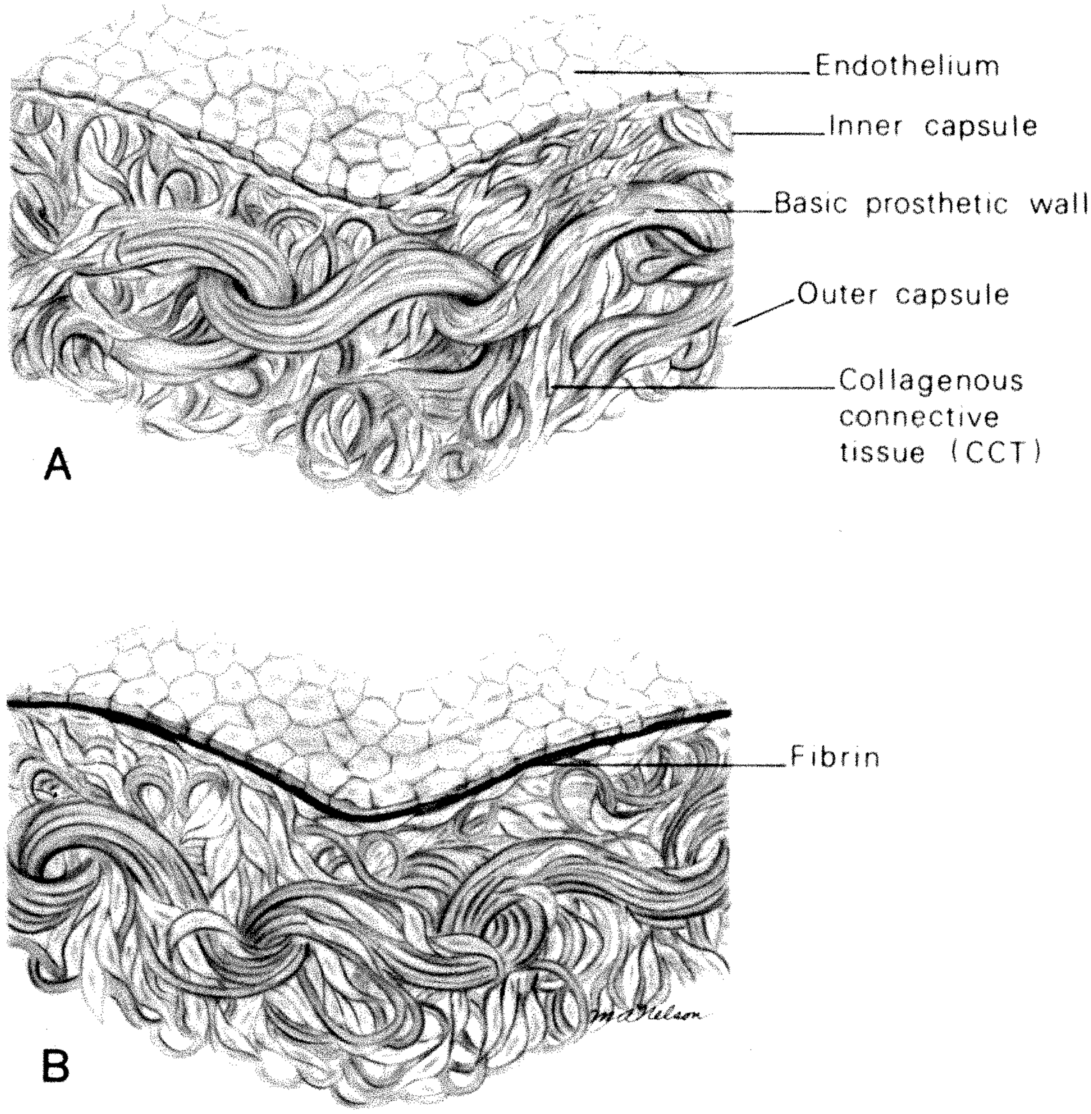

FIG. 1. Diagrammatic representation of the term "complete healing" of a vascular prosthesis wall, as used in this paper. Complete healing means that the wall of the graft is completely encapsulated in fibrous tissue, and that the flow surface is covered by endothelium. The endothelium may be lying directly on the CCT (A), or there may be a layer of fibrin beneath it, no more than the equivalent of a few cells thick (B).

The distance of the endothelium from the suture line was not specified.[2] In the prosthesis herein reported, patches of complete healing were demonstrated all along the 45 cm length of the prosthesis, and we therefore believe this case to be highly significant.

Case Report

The patient, a fragile 75-year-old Caucasian man, when seen by us on the 14th of May, 1971, had severe rest pain and impending gangrene of his right foot, as well as signs of severe ischemia of his left foot. Femoral pulses were weak, particularly on the right, and systolic murmurs were present at both groins and over the iliacs. No pulses were palpable below the groin. Translumbar aortography showed severe bilateral aortoiliac stenosis that was greater on the right than on the left, bilateral superficial artery occlusion, diseased but patent popliteals, and extensive occlusive changes in the run-off vessels of the lower leg. We considered this patient a poor risk for an aorto-bilateral common femoral artery bypass graft because of his advanced age, general fragility, and poor physical condition, which included hypertension, emphysema, coronary heart disease and extensive radiation fibrosis of the right side of the abdomen secondary to radiotherapy administered in 1948 for cancer of the right testicle. Because of these risk factors, we elected to perform a left axillary-bilateral common femoral artery bypass graft. The procedure was performed on May 26, 1971, using a 6mm diameter random-crimped prosthesis of knitted Dacron with an external velour surface (USCI, Inc., of Billerica, Mass.)

The patient tolerated the axillary-femoral procedure without difficulty and was discharged on the ninth postoperative day with markedly improved circulation of both lower legs and feet. For the ensuing 20 months, he was able to walk for 3 to 4 blocks (the limit of his general strength) without claudication and his feet remained viable and painless. Then, in late January 1973, the patient began to fail rapidly and after a few days developed severe abdominal pain. When brought to the hospital by ambulance he was in a near-terminal state on February 1, 1973 with evidence of congestive failure, small bowel obstruction, and peritonitis. The graft was patent, as indicated by pulsations along its course.

Although the risk of abdominal exploration was considered very high, the outlook without correction of the intra-abdominal pathology appeared hopeless. As the abdomen was opened, profound circulatory collapse occurred. Unsalvageable mesenteric infarction was present and the patient expired shortly. Permission was obtained from the family for removal of the graft in the operating room. The graft was exposed through a continuous incision along its entire length. Perigraft tissues were very securely attached to the wall, forming a flexible outer capsule that blended into the perigraft tissues without a distinct boundary.

The entire graft, including the anastomoses to the axillary and common femoral arteries, was removed within 30 minutes of death. It was then flushed gently with 5% dextrose and water and carefully opened throughout its length. Postmortem thrombus had formed to cover the flow surface in some areas, but not in others. The surface where postmortem thrombus had not formed was glistening, smooth, whitish, and sufficiently thin (circa 100 microns) that the fibers on the underlying prosthetic wall could be seen. Thrombus that was obviously postmortem was gently removed from the other portions of the graft, revealing the underlying wall in these areas to be thicker and less translucent than in those areas where postmortem thrombus had not formed.

The graft was then submerged in 0.25% silver nitrate for two minutes. The elapsed time between the patient's death and silver nitrate staining for endothelium identification was approximately one hour. After completion of the silver stain, the flow surface was scanned under the stereomicroscope and the specimen placed in 10% formalin. After fixation, the flow surface was studied from one end to the other under the stereomicroscope and the location of the endothelium was accurately mapped on a scaled reproduction of the opened graft (Fig. 2). Photographs of the flow surface were taken at points near the upper anastomosis, and in the middle of the graft, where they were taken in areas representative of non-endothelial coverage as well as in areas representative of endothelial coverage.

Tissue blocks were cut from many areas, including those areas photographed to document the presence or absence of endothelium. These blocks were fixed for histologic study, and sections stained with hematoxylin and eosin and Masson's trichrome. Examination of these sections showed that endothelium was present only in those areas where full fibrous tissue encapsulation had occurred. Endothelium lay both on the collagen itself and on a very thin layer of fibrin on top of the collagen. Surface and cross sectional findings from the graft locations indicated in Fig. 2 are shown in Figs. 3 through 6.

Complete healing was present not only in the proximal portion of the graft adjacent to the axillary artery (Figs. 3 and 4), but also in islands, scattered throughout the length of the graft (Figs. 3 and 5). Thirty-two per cent of the flow surface of the prosthesis was covered by endothelium, as measured by planimeter on the scale drawing.

In contrast to the healing shown in Figs. 3, 4 and 5, Fig. 6 shows an area of incomplete healing, representative of 68% of the graft surface, from location "h" (Fig. 2) in the midst of an endothelial island. In these areas, although there was fibrous tissue ingrowth the full thickness of the graft wall, including a layer covering the inner surface of the fabric, this tissue was nonetheless beneath a layer of compacted fibrin approximately 0.25 mm thick, which formed the flow surface.

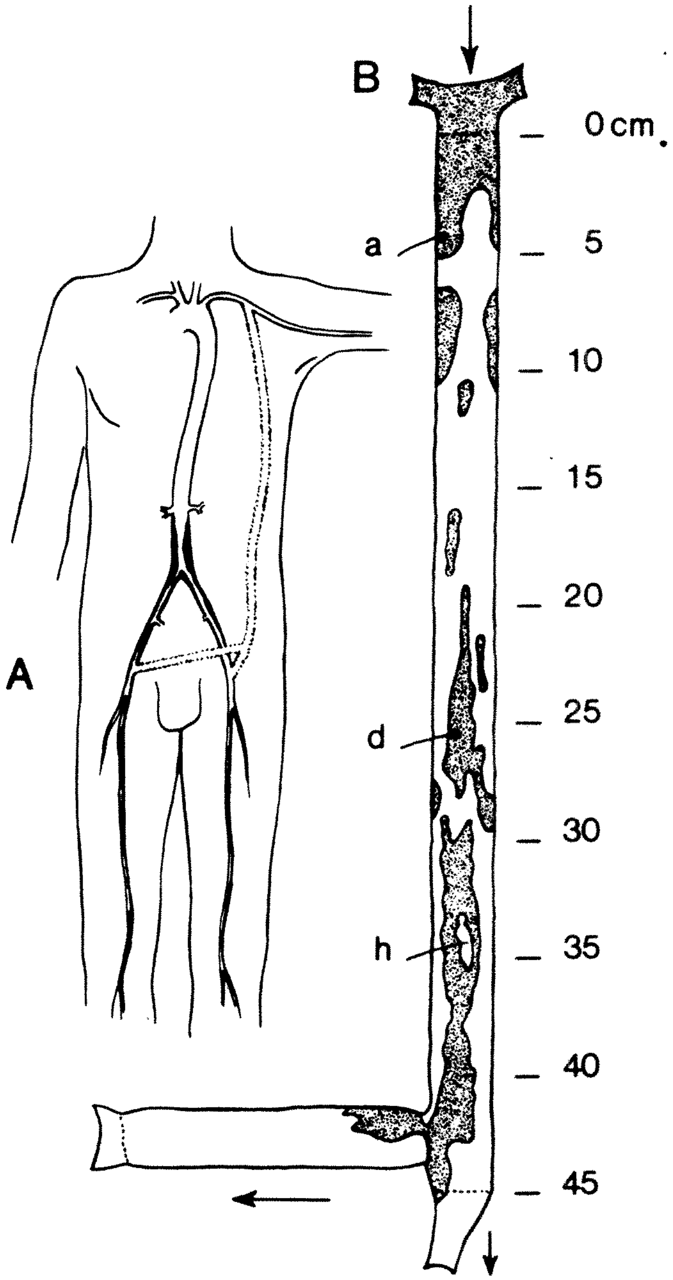

FIG. 2. (A) Location of left axillary bilateral common femoral external velour bypass prosthesis. (B) Surface tissue map of graft after recovery from patient 20 months postoperatively. Stippled areas indicate tissue. "a": pannus at proximal end; "d": island of tissue covered by endothelium; "h": area of tissue covered by thin red thrombus.

Discussion

The extraordinary thrombus-resistant characteristics of an intact, healthy endothelial flow surface make it the desired lining for a prosthetic arterial graft. Unfortunately, such a flow surface is exceedingly difficult to obtain on arterial prostheses in man. In fact, until we observed the prosthesis reported in this paper, we were not certain that an endothelialized flow surface on top of a fibrous tissue base was an attainable objective in man. It is reassuring to know that complete healing is possible with current prostheses, even if it is a slow and unreliable process.

Our human specimens of the external velour prosthesis show that it takes about 3 to 5 months for perigraft collagenous connective tissue to penetrate the interstices of these prostheses to form a luminal fibrous tissue layer. At first, this layer is discontinuous and patchy. It may not become fully continuous until about two years have passed, or ever, for that matter. Our observations of smooth-walled prostheses are too few in the 3 to 5-month period to allow a comparison of healing with the velour or filamentous type of graft for this time of implantation.

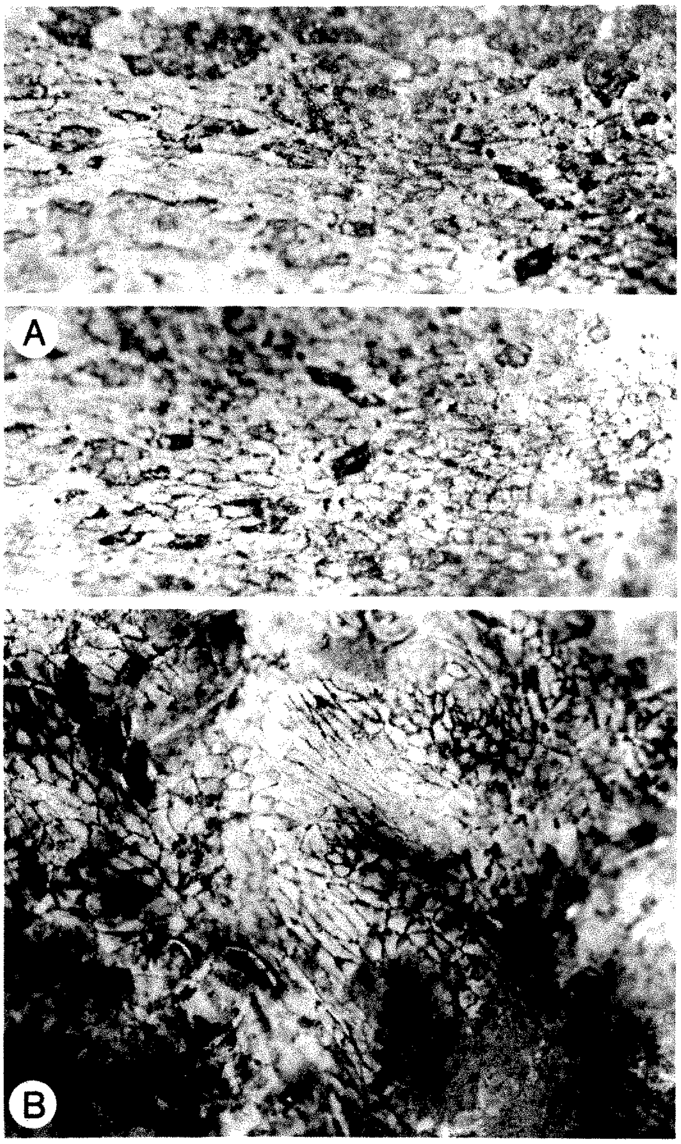

FIG. 3. (A) Surface photographs of endothelium near distal edge of pannus "a" in Fig. 2. (B) Endothelium at "d" in Fig. 2. Coverage is thin and translucent. Note underlying knit pattern and fibrils of fabaric.

Our objectives now are to determine how to assist man in healing porous arterial prostheses in a more reliable and rapid manner. In earlier papers,[4–7] we compared the design of the wall of current porous arterial prostheses, which seems to have an important effect upon healing, particularly in man. In comparative healing studies of specimens beyond 3 to 5 months we have found that the filamentous (external) velour prosthesis, as observed in this case report, heals more rapidly and completely than do conventional knitted porstheses with relatively smooth walls. It appears that cells are better able to migrate on a trellis of loosely-knit filaments than through a wall composed of tightly compacted fiber bundles.

We believe that the full potential of the trellis concept of graft construction embodied in the filamentous design of the prosthesis being reported has yet to be achieved, and that this design should be investigated further. The findings herein reported are encouraging, as they indicate that it is possible for man to completaely heal a filamentous velour knitted artrial prosthesis, whereas our previous findings[1] indicated that man apparently cannot completely heal a smooth-walled knitted prosthesis. Even with the filamentous prosthesis, the process of healing is too slow and erratic. Of the two cases in which we have reported complete healing, the short-term graft (182 days) showed more even healing than the longer-term graft (20 months). A prosthesis is no stronger than its weakest link, and if it is incompletely healed in some areas, it remains liable to thrombotic closure.

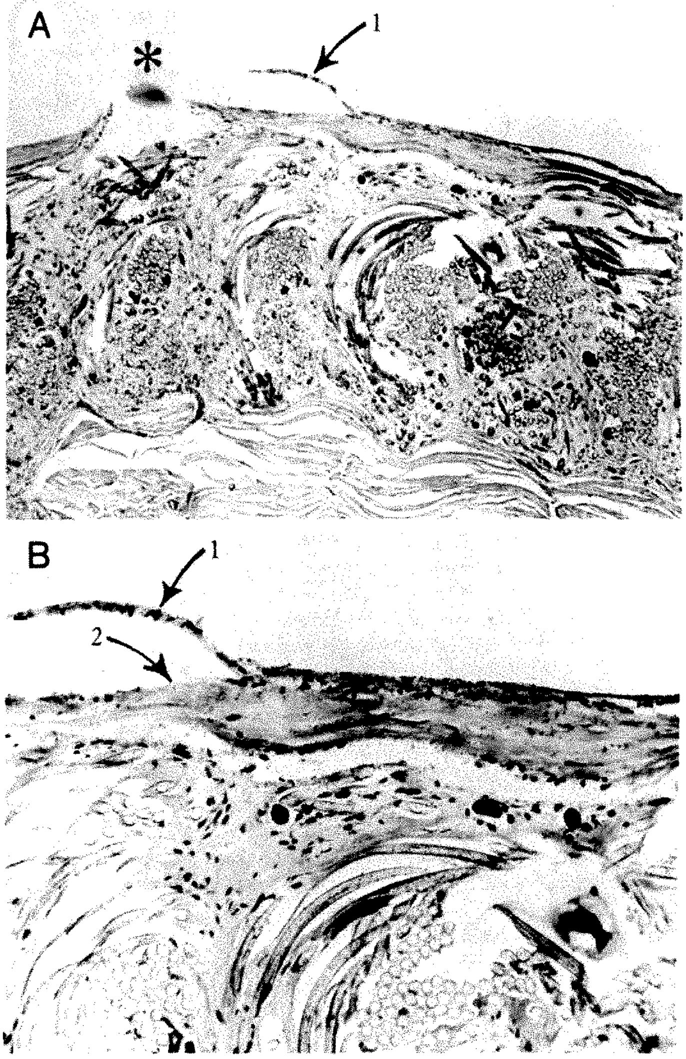

FIG. 4. Sections through "a" of Fig. 2.. A: Section through area photographed in Fig. 3A. Thin tissue present at cutting artefact (*). Capsular formation and transinterstices growth are similar to that shown in Fig. 5. Endothelium has fortuitously lifted (arrow #1). (B) Higher magnification at arrow #1 shows endothelial cell nuclei and silver-stained intercellular "lines." Arrow #2 points to collagen on which the endothelium rested. Elsewhere in same section there is a thin layer of fibrin between the endothelium and the fibrous tissue.

There is need for better prostheses for the large and medium caliber arteries. And unless grafts can be substantially improved, they will not serve as successful substitutes for small caliber arteries such as the tibials and coronaries.[3,4] But the evidence presented in this paper suggests that we should maintain some optimism concerning the development of successful arterial prostheses for small caliber vessel replacement.

Summary

For the first time, we have seen in man areas of complete healing of an arterial prosthesis at points far removed from the anastomoses. (We define complete healing as full wall fibrous tissue encapsulation with a flow surface of endothelium.) Complete healing was observed scattered throughout the length of a knitted Dacron prosthesis with an external velour surface that had been implanted for 20 months as a left axillary-bilateral common femoral artery bypass graft. This observation indicates that complete healing of a porous arterial prosthesis is an attainable goal for man. The filamentous wall of the prosthesis reported in this paper appears to have been of substantial aid to the advanced healing observed. However, the fact that complete healing was not continuous throughout the length of the graft indicates that additional means of accelerating healing must be sought.

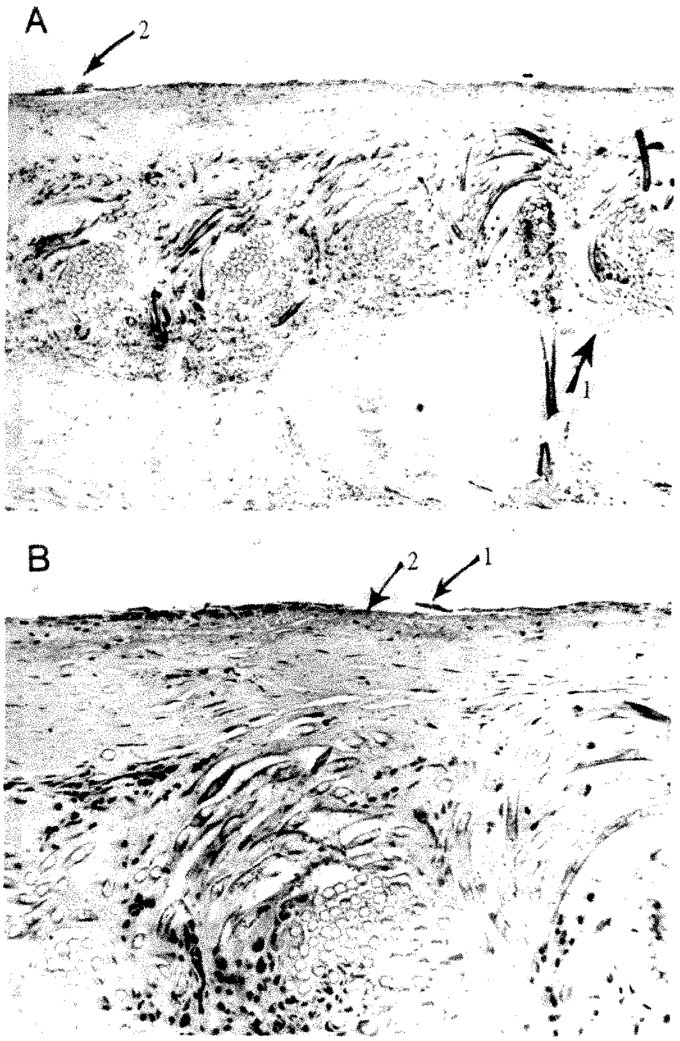

FIG. 5. (A) Section at island "d" of Fig. 2 shows fibrous inner and outer capsules with well-established bridges through the interstices. Note external velour fibrils locked in outer capsular fibrous tissue (arrow #1), accounting for firm bonding. The inner capsule is variably surfaced with thin fibrin (arrow #2) and endothelium. (B) Higher magnification showing fragmented silver-stained endothelial layer at arrow #1. The endothelium rests upon a thin layer of compacted fibrin (arrow #2) which is still undergoing fibroblastic organization.

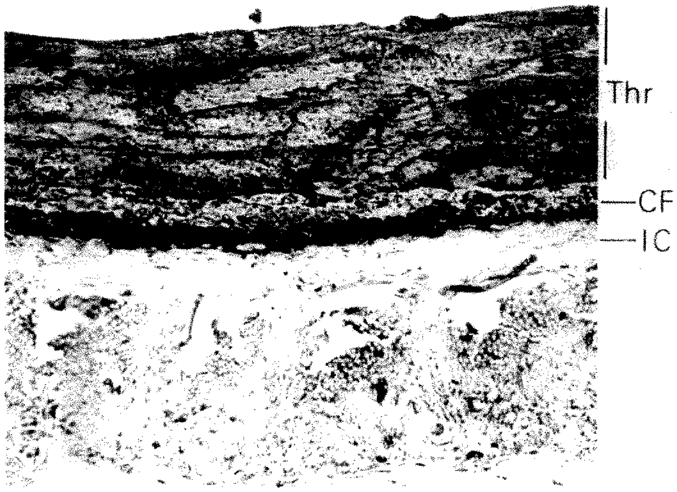

FIG. 6. The white areas of the tissue map (Fig. 2) showed varying degrees of organization and thrombotic coverage. Here at "h," a tissue inner capsule (IC) has formed. This, in turn, is surfaced by a layer (black at CF) of compacted fibrin. This compacted fibrin is covered by a more recent layer of laminated whole thrombus, here 0.5 mm thick. In other sections, the luminal aspect of the fabric was covered solely by compacted fibrin with organization only part way through the interstices.

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Infection in War Wounds:

Experience During the 1973 October War in Israel

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The development of infections in 420 wounded soldiers, admitted to the Hadassah University Hospital in Jerusalem between October 7, 1973 and November 31, 1973, was studied. An attempt was made to relate the development of infection to the type of injury. The overall infection rate was 22%, but varied with the type of injury. Three "risk factors" were found to be associated with infection regardless of the number of injuries: 1)penetrating abdominal wounds involving the colon; 2) fractures involving the femur; 3) burns involving more than 25% of body surface. In patients with comparable injuries, the presence of infection was found to prolong the duration of hospitalization. Pseudomonas was the most common single pathogen. There were no cases of myonecrosis (gas gangrene). Of the 8 soldiers who died, 5 died with or because of infection.

PRIOR TO THE OUTBREAK of war in Israel in October 1973, an active surveillance program of nosocomial infections had been functioning in the Hadassah Hospital in Jerusalem. When the first war casualties started reaching the hospital, it was decided to use the surveillance team in an effort to control the spread of infections in these patients. The activities of the team, which consisted of two nurse-epidemiologists, and two physicians (the hospital epidemiologist and microbiologist), were planned with the objectives of earliest possible detection of infection, rational use of antibiotic therapy, and maximal efforts to prevent cross infection.

This paper presents an analysis of infections occurring in these war casualties, based on the information gathered by the team.

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Materials and Methods

Subjects and Data Collection

The 420 war casualties admitted to the wards of the Hadassah University Hospital between October 7, 1973 and November 31, 1973, form the subject of this report. This population was not randomly chosen. It consisted of wounded soldiers who had survived the first 12 to 24 hours after injury. They had all received battlefield first aid treatment which included administration of penicillin within 30-60 minutes after injury, and most had had further medical and surgical care at the battle-field clearing hospital. They were transferred to the Hadassah Hospital according to a system employed by the army medical authorities for the distribution of casualties. The basis of this system was to spread the work-load over several hospitals, with the more severe casualties being transferred to the better-equipped and staffed hospitals.

Our material is thus a representative sample of the more severe casualties, mostly the victims of high velocity missiles or burns, seen in this war. Casualties transferred to Hadassah from other secondary hospitals are not included in this report. A chart was opened by the nurse epidemiologist on every soldier admitted to the hospital wards. The patients were then followed for a period of three months, or until discharged from the hospital. The nurse epidemiologist visited the wards and the Bacteriology laboratory daily, and recorded informa-

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tion relevant to the possible development of infection including temperature, antibiotic therapy, the introduction of urinary catheters, intravenous therapy, etc. From the Bacteriology laboratory work sheets, the results of the latest cultures, together with antibiotic sensitivity tests, were recorded. The two physicians visited the wards daily and consulted with the surgical staff about patients suspected of having developed infection, or those known to have clinically overt infections.

At these daily meetings, decisions were made with regard to diagnosis, treatment, isolation procedures, and general measures to prevent the spread of infection in the wards. The decisions reached at these meetings were passed on regularly to the nurse, to update her records. The information presented in this paper was obtained from the data sheets completed by the nurse, and is thus based on data which were recorded objectively, and on a clinical followup of the patients.

Definitions of Infections. The following definitions were used: **Infection:** this term is used to denote the presence of clinically overt signs of disease produced by the presence and multiplication of bacteria. It is not used to denote microbial invasion and multiplication alone. **Infection at the site of injury:** includes both wound infection and infection in an internal organ directly related to the site of injury. **Infection at another site:** the presence of infection occurring at any site other than that of the specified injury. **Wound infection:** the presence of a purulent discharge, with or without bacteriological findings. **Infected burns:** the presence of signs of infection locally in the burn, together with systemic signs such as fever and malaise. Because of the frequent colonization of burns by pathogenic bacteria, the presence of positive cultures was not sufficient on its own for a diagnosis of infection (see definition of *Infection* above). **Abdominal infection:** infection in the abdominal wound or intraabdominal infection. **Septicemia:** positive blood cultures in patients showing clinical signs of systemic infection. **Urinary tract infection:** the presence of symptoms such as dysuria and frequency, together with at least two consecutive urine cultures of 10^5 or more bacteria per ml. (In paraplegic patients, with no symptoms and with an indwelling catheter, the presence of pyuria together with at least two consecutive urine cultures of 10^5 bacteria per ml was accepted as evidence of a urinary tract infection).

Classification of Injuries. The patients were classified, according to the type of injury sustained, into the following groups: 1) Burns; 2) Penetrating abdominal injuries; 3) Fractures (excluding skull); 4) Penetrating chest wounds; 5) Amputations; 6) CNS injuries with para- or quadraplegia; 7) Fractured skulls; 8) Soft tissue injuries. While almost all the injuries in the first seven categories had some soft tissue involvement,those in which there was only soft tissue involvement were placed in this separate group; 9) More than three of the above types of injury: this constituted a group with the most extensive injuries.

Analysis of Results

Factors that were associated with an increased risk of developing infection were analyzed in terms of relative risk using the method described by Mantel and Haenszel.[12] This method measures the association between the disease and the factor under study by comparing the occurrence of disease in persons with and without the specified characteristics. The Relative Risk is the ratio of the cross products in a 2 x 2 table. A ratio of more than 1 is regarded as a positive association, less than 1 as a negative association, and 1 as no association. A contingency χ^2 test was also employed to establish a P value.

In order to establish whether infection affected length of stay in hospital or vice versa, we employed a matching procedure: patients who had developed an infection early during their hospitalization (up to 10 days) were matched with patients who did not develop an infection, and who had combinations of injuries as close to those of their counterparts in the infected group as was possible. Thirty-eight pairs matched by this procedure were included in the sample, and a wide range of injury types was represented. (The only type of injury not included was burns of 25% and over, since they were always associated with infection, and could not be matched.) The pairs were compared in terms of two parameters, length of hospitalization and age. The nonparametric Wilcoxon signed rank test was employed for the statistical analysis.[14]

Bacteriology

Routine cultures at fixed time intervals were not taken, but wounds were cultured repeatedly. When infection was diagnosed clinically, a decision as to the causative organism or organisms was based on an assessment of the bacteriological findings in specimens related chronologically to the time of appearance of the clinical signs of infection.

Results

Rates of Infection According to the Type of Injury

Of the 420 soldiers included in this report, 276 had one type of injury and the rest had more than one type. (Those who had sustained only one type of injury did not necessarily have a single injury, for example multiple fractures will appear as one type of injury i.e., fractures).

Twenty-two per cent of the 420 were found to have developed an infection during their hospitalization. These 94 soldiers had 133 infectious episodes: 66 had a single infection, and 28 had more than one.

All except four of the single infections occurred at the site of injury. The four exceptions were two urinary tract infections, one case of otitis media, and one of

TABLE 1. *Rates of Infection at the Site of Injury and at Other Sites by Type of Injury*

Type of Injury	No. of Patients	*Infection at Site of Injury* No. of Patients	*Infection at Site of Injury* Rate %	*Infection at Other Sites* No. of Patients	*Infection at Other Sites* Rate %	Overall Rate of Infection %
Burns	49	17	35	2	4	39
Penetrating Abdomen	53	16	30	8	15	45
Fractures	99	18	18	14	14	32
Pent. Chest	50	6	12	7	14	26
Amputations	19	6	(32)	5	(26)	(58)
Paraplegia	8	3	(37)	3	(37)	(74)
Skull	19	–	–	1	(5)	(5)
Soft Tissue	178	10	6	–	–	6
3 or More of the Above	55	29	53	–	–	53

Figures in parenthesis are based on less than 20 patients.

pneumonia. The patients with multiple infections, all had infection at the site of their injuries, but some also had infections at other sites: ten had septicemia, four had urinary tract infection, and two had pneumonia.

Infection rates varied a great deal with the type of injury sustained. Table 1 summarizes the rates of infection by type of injury. With the exception of those injuries in which the numbers were too small, the highest rates of infection were seen in the group with more than three types of injury (53%) and in penetrating abdominal wounds (45%) and burns (39%). Almost all the burned patients with infections developed their infections in their burn wounds. Similarly, two-thirds of the infections in patients with penetrating abdominal injuries were at the site of this injury, and more than half of the infections in patients with fractures, occurred at the fracture site. On the other hand, in patients with penetrating chest injuries, less than half of the infections were at the site of this specified injury, the others being at the site of other, mainly soft tissue injuries, which these patients had sustained.

In patients with only soft tissue injuries, the infection rate was low, and all infections occurred at the site of injury.

In patients with three or more types of injury all had infections at the site of one of their injuries, but 4 patients had in addition urinary tract infections. Three of 8 patients with para- or quadriplegia developed urinary tract infections. All 10 urinary tract infections occured late in the course of the hospitalization, and were always in catheterized patients.

Six of the patients with amputations developed infection at the amputation site, and 5 developed infections in soft tissue injuries at other sites.

Association Between Some Specific Injuries and Infection

The association between certain types of injuries and increased risk of infection is shown in Table 2. Among the penetrating abdominal injuries, a significant difference was found between those patients in whom there was perforation of the large bowel, and those without such perforation. Those with a perforated colon had four times the infection rate at the site of injury of those without (58% and 14%, respectively), or in terms of relative risk, the risk for infection was 8 times higher for those with a perforated colon. When, however, abdominal infections were excluded, there were no significant differences in the rates of infection at other sites (Table 2). Of the 19 patients with colon involvement, 8 (40%) had infections elsewhere, whereas of 34 patients without colon involvement, 10 (30%) had infections at other sites. The difference is not significant. Burns involving 25% or more of body surface, had 100% infection rate, as compared to 14% in burns of less than 25% of body surface. The relative risk was 76.8 higher for the former group. When infections at the burn site were excluded, there were no differences between the two groups with regard to infections at other sites (Table 2). Fractures involving the femur had nearly three times the rate of infection of fractures of other bones. In terms of relative risk, those with fractures of the femur had nearly four times the risk of developing an infection as compared to those without fractures of the femur. When infections at the fracture site were excluded, there was no difference between the femur and the non-femur groups in the incidence of other infections. Multiple fractures had only slightly more infections than single fractures. The differences, however, were not significant. When those with more than three types of injury, including at least one of the above risk factors, were compared with those with the same extensive injury but without any of the risk factors, the relative risk of developing infection was 23.3 times higher for the former group. Single soft tissue injuries had a higher infection rate than multiple soft tissue injuries, but the difference was not significant.

Infection in Relation to Length of Hospitalization and Age

Length of stay in hospital varied a great deal with the type and severity of injury. Some patients with soft tissue injuries were in hospital for three days only, while the

TABLE 2. *The Association Between Some Specific Injuries and Infection*

Type of Injury	Total No. of Patients	*Infection at the Site of Injury* Rate (%)	RR*	P (contingency χ^2)	*Infection at Other Sites* Rate (%)	P (contingency χ^2)
Penetrating Abdomen						
Involving colon	19	58	8.0	< 0.001	40	N.S.
Not involving colon	34	14			30	
Burns						
$> 25\%$ Body surface	12	100	76.8	< 0.001	17	N.S.
$< 25\%$ Body surface	37	14			11	
Fractures						
Involving femur	20	40	3.7	< 0.05	20	N.S.
Not involving femur	79	15			18	
Single fractures	38	18	1.6	N.S.	10	N.S.
Multiple fractures	41	12			7	
Soft Tissue						
Single injuries	69	8	2.5	N.S.	—	—
Multiple injuries	109	4			—	—
Patients sustaining more than 3 types of injury						
Involving colon and/or $> 25\%$ burns and/or fracture of the femur	15	93	23.3	< 0.001	—	—
Without colon involvement or $> 25\%$ burns or fracture	40	38			—	—

*Relative Risk
N.S. = not significant

average stay for patients with a penetrating abdominal injury was 66 days. Patients with para-plegia were only followed for 93 days, but their hospital stay usually extended to many months. In order to establish whether infection affected length of stay, we compared 38 pairs of patients matched by their combination of injuries, and found a highly significant difference in terms of length of stay between those who became infected early during their hospitalization and those with the same combination of injuries who did not develop an infection during their hospitalization. The difference is apparent even when the means are compared, 51 days for the infected and 34 days for the non-infected. However, because of the range of variation within each group (3-93 days), we used the non-parametric Wilcoxon test, which ranks the differences within each pair. This yielded a P value of <0.0003 (Table 3). Infected soldiers tended to be older than non-infected soldiers, but the difference was not significant.

Bacteriological Findings

Two hundred and forty-four bacterial species were isolated from the 133 infectious episodes in 94 patients. The distribution of these bacteria by the site of the infection from which they were isolated is shown in Table 4. (The figures in this Table refer to the number of times each organism was held to be responsible for the infection listed and not the number of times it was isolated.)

Pseudomonas was the most common single species

TABLE 3. *Differences in Length of Stay in Hospital and Age, Between Infected and Non-Infected Patients Matched for Type of Injury*

	No. of Matched Pairs	*Mean Values* Infected	Non-infected	Normalized Wilcoxon statistic for differences between infected and non-infected Z	P
Length of stay in hospital	38	51 days	34 days	16.2	< 0.00003
Age	29*	25.6 yr	24 yr	1.4	N.S.

*In 9 pairs the age was not known for at least one of the pair
N.S. = not significant

TABLE 4. *Distribution of Bacteria by Site of Infection.**

Bacteria	Type of Infection Abdominal	Burns	Fractures	Soft Tissue	Septicemia	Thoracic	Urinary Tract	Others	Total	%
Bacteroides	9	–	2	1	–	–	–	–	12	5.0
Enterobacter	3	4	5	3	1	2	–	–	18	7.4
E. coli	14	1	5	3	3	2	2	3	33	13.5
Klebsiella	7	11	3	3	5	1	6	1	37	15.0
Proteus	–	–	4	4	–	–	–	1	9	3.7
Str. faecalis	4	6	6	6	1	1	–	–	24	9.8
Staph. aureus	–	8	6	4	1	–	–	1	20	8.2
Staph. albus	–	1	1	1	–	2	–	–	5	2.0
Pseudomonas	8	19	12	12	4	1	2	6	64	26.2
Candida	–	1	1	–	2	–	–	1	5	2.0
Clostridia	–	–	–	2	–	–	–	–	2	0.8
Other Gram negative rods	1	2	2	5	1	1	–	–	12	4.9
Str. hemolyticus	–	–	–	2	–	–	–	1	3	1.2
Totals	46	53	47	46	18	10	10	14	244	100.0

*Figures refer to number of times the organism was responsible for the stated infection.

(25% of the total number). One-third of all Pseudomonas infections were in burns. Thirty six percent of the pathogens isolated from infected burns were Pseudomonas as were 25% of the pathogens causing infection in fractures and soft tissue. The Pseudomonas infections all developed some time after admission to hospital. The earliest Pseudomonas infection in burns was seen on the tenth day after the first admission, and in fractures on the 14th day. This pattern of late appearance of Pseudomonas infections was seen in three different wards (plastic surgery and two orthopedic wards).

Klebsiella was the second most frequent organism responsible for infections in these patients (15% of the total number). In the plastic surgery ward, Klebsiella was isolated on the sixth day after the first admission. On the tenth day a resistant strain of Klebsiella appeared (resistant to all antibiotics except Colistin). Between the 17th of October and the 29th, 9 patients, all of whom had burns of more than 25% body surface, were infected with this strain. These infections were associated with severe morbidity and one mortality. This episode was the only proven example of a hospital-acquired cross infection in this series.

Bacteroides made up 5% of the pathogens, and were mostly involved in abdominal infections. Nine of the Bacteroides infections were in patients with penetrating abdominal wounds with colon involvement. Twenty percent of the pathogens isolated from abdominal infections were Bacteroides species.

Candida species were not common (2% of the total), but were responsible for two episodes of septicemia.

Clostridia species were responsible for only two soft tissue infections neither of which showed evidence of myonecrosis.

There were three infections with β hemolytic streptococci, all in patients with soft tissue injury only.

Septicemia

There were altogether 12 episodes of septicemia occurring in 10 patients. Five of these patients died with clinical signs of septicemia. Five of the septicemic episodes developed in patients with infected burns, three in patients with abdominal infections, two in patients with central nervous system and multiple soft tissue injuries. Klebsiella was isolated from 5 of these episodes, Pseudomonas from four, *E. coli* from three. The two Candida septicemias were secondary to IV catheterization.

Mortality

The mortality rate in this group of patients was 2% (8 out of 420). Five of these deaths, as mentioned above, were associated with severe infections and evidence of septicemia. There was no definite evidence of infection at the time of death in the other three fatal cases. In four of the fatal cases, the septicemia originated from infection at the site of injury—intra-abdominal infection in two cases, soft tissue injury and burns in one case each. The fifth fatality developed a pre-terminal pneumonia, which was presumably the source of the septicemia. All 5 had severe multiple injuries and in at least two these were probably incompatible with survival—one had more than 70% burns, and the second had multiple abdominal visceral injuries including severe pancreatic damage. The three fatalities without definite evidence of septicemia all had severe central nervous system or abdominal injuries that were incompatible with life.

Discussion

This study indicates that it is possible to predict what type of war injury is particularly predisposed to infection, and to identify high risk factors within certain types of injury.

While the overall infection rate in this group of war casualties was 22%, the rate varied considerably with the type of injury. Three factors that were associated with a particularly high risk of developing an infection were penetrating abdominal wounds involving the large bowel, burns of 25% of body surface or more, and fractures of the femur.

The association between these risk factors and infection is strengthened by the fact that when the most extensively injured group was divided into those with any of these risk factors and those without, rates of infection were 2.5 times higher for the former, and the relative risk of developing an infection was 23 times higher.

The increased risk of infection when penetrating abdominal wounds involve the colon is not surprising, in view of the rich bacterial flora in this organ and the tissue contamination which must inevitably follow perforation of this portion of the intestine. The causative organisms were always those occurring as part of the normal colonic flora.

The high infection rate in severe burns is also not surprising. The association between fractures of the femur and a high infection rate was unexpected, and the reason for this association less obvious. Infection is generally more common in wounds of the lower rather than the upper extremities, but this does not explain the association with fractures of the femur as opposed to the tibia. The inevitable presence of more extensive soft tissue destruction in association with fractures of the femur as opposed to those of the lower leg, may be an important factor.

The absence of an association between a high risk of infection and certain types of injury is worthy of comment. When fractured femurs were excluded, multiple fractures did not significantly increase the risk of infection when compared to to single fractures. The rate of infection in penetrating chest injuries (12%) and penetrating abdominal injuries not involving the large bowel (14%) was much lower than in abdominal injuries involving the colon (58%) and is related to the lack of contamination by normal flora in the former two types of injury. The apparent anomaly of single soft tissue injuries having twice the rate of infection of multiple injuries is explained by the fact that most multiple soft tissue injuries were superficial small shrapnel wounds, whereas the single injuries involved extensive loss of tissue due to larger shrapnel particles or high velocity missiles.

There is little in the published literature with which to compare our experience. In their series of 83 penetrating abdominal injuries in Vietnam, Getzen, et al.[7] described an infection rate of 10% in 21 patients with colon involvement, 14 of whom had only colon injury. This figure is much lower than the 58% infection rate that we found in 19 patients with colonic involvement. The difference may be partly explained by the fact that in the Vietnam series a decision as to the presence of infection was based on a retrospective review of case records, whereas in our series the diagnosis of infection was made at the bedside on the basis of both clinical and laboratory findings. Records, especially under war conditions, may lack information which is not vital to the surgeon at the time, but may be essential for retrospective assessment. This impression is supported by the number of unexplained temperatures, which Getzen et al.[7] could not classify. Another reason for the differences between their infection rate and ours is related to definition. We classified under abdominal infection both wound and intra-abdominal infection, while in the Vietnam series the authors separated wound from intra-abdominal infection, which they classified under morbidity, together with other types of surgical complications.

Christy[5] reviewed 19 cases with combined bone and bowel injuries in Vietnam, and noted a special risk of infection with this combination. Reviewing Christy's paper showed that all 16 patients in this series who developed an infection had a penetrating injury of the colon, while the only two patients without bacterial infection had only small bowel involvement. It is therefore more than likely that the very high infection rate in his series was associated with perforation of the colon, an assciation which was also striking in our series.

Another aspect of morbidity which we investigated was length of stay in hospital. This varied with the type of injury from three to 93 days. The data from the matching procedure which we used suggest that the presence of infection prolonged the duration of hospital stay rather than that extended hospitalization increased the risk of development of infection.

Infected patients seemed to be slightly older than non-infected, but the differences were not significant.

We tried to establish whether the length of time between injury and receipt of medical care was associated with the development of infection, but information was available for only 31 out of the 76 patients in our matched sample. All of these, both infected and non-infected, received their initial medical care within 30 to 60 minutes of injury. There was, however, no information available about the type of initial medical care received by the two groups, other than that all received the same early antibiotic treatment with penicillin.

Bacteriology

In contrast to findings during the Second World War[3] or during the Korean War,[11] we found a low frequency of clostridial infections, due to the early and adequate surgical treatment including debridement, and the routine early administration of penicillin G to all cases with tissue destruction (in practice, all the injured). Early administration of penicillin is also responsible for the low frequency of hemolytic streptococcal infections, and probably accounts for the low rate, in general, of early infection in the first week after injury. It also almost certainly determined the nature of the causative organisms of the late infections, predominantly Gram negative bacteria, many of which are known to be responsible for nosocomial infections in this hospital during peace time.

Tong[16] described the bacterial flora of war wounds of the extremities in a Naval Hospital in Vietnam, and found a predominance of Gram negative bacilli, especially Pseudomonas, Enterobacter and Proteus, by the fifth day after injury. These findings were based on routine swabbing of wounds, not necessarily related to the presence of clinical signs of infection, on the first, third and fifth post-injury days. We did not perform routine cultures, and specimens were only collected when there was clinical evidence of infection. This may explain why these Gram negative organisms appeared later in our series. *Pseudomonas aeruginosa*, for example, first appeared in the burn unit ten days after the first admission but then never disappeared from that unit. A similar pattern was repeated in the orthopedic ward where Pseudomonas appeared 14 days after the first admission. It accounted for a quarter of all isolates responsible for infections at fracture sites. This is a lower figure than mentioned by Heggers et al.,[9] who found that 46.9% of all isolates from orthopedic war wounds were *Pseudomonas aeruginosa*. The late appearance of Pseudomonas suggests that prophylactic vaccination started soon after injury, should be considered as a possible future measure in the prevention of infections by this organism in certain war injuries. Although the evidence for its efficacy is not yet conclusive, such vaccination had been used in burns[1,2] and against respiratory infections.[13]

We found that 58% of injuries involving the colon were infected at the abdominal site, and three-quarter of these infections were associated with Bacteroides. None of the infections in penetrating abdominal wounds not involving the colon were caused by Bacteroides. This finding is consistent with the frequency with which Bacteroides is found in the colon compared to the small bowel. Fullen, Hunt and Altmeier[6] and Thadepalli et al.,[15] suggest that preoperative prophylaxis in penetrating abdominal woulds reduces infection rate considerably, and the question therefore rises as to whether antibiotics active against *Bacteroides* should not be used from the earliest possible moment in patients with penetrating abdominal wounds. We feel that it might be advisable to administer a combination of clindamycin and gentamicin to all abdominal injuries at the time of injury. If the presence of colonic involvement is proven at laparotomy, the treatment could be continued for 48-72 hours. If no colonic involvement is demonstrated, treatment can be stopped. This short term use is unlikely to lead to adverse side effects.

In relation to the detection of cross infection among the wounded, we were limited by the fact that under war conditions pyocine, bacteriophage or serotyping of bacteria could not be carried out. Our one definite experience with cross infection was a strain of Klebsiella which was resistant to all antibiotics except colistin and which spread rapidly through the burn unit. It first appeared on the tenth day after the first patient was admitted to the ward. During the following 12 days, 9 patients developed infections with this strain. All these patients were removed to a room set aside for this purpose, and a program of isolation and barrier nursing introduced. Intensive antibiotic therapy with colistin alone was instituted, and all other antimicrobial agents stopped in these patients. After a week the strain disappeared, and this sensitivity pattern was not seen again either in strains of *Klebsiella* or of other Gram negative bacteria.

We have related risk of infection to type of injury, but have been unable to relate it to severity because there are no criteria available for grading severity. Baker et al.,[4] have suggested a grading system based on a severity scale for each body area involved, and related the composite score for all body areas, to mortality. They were concerned with automobile accidents, where most injuries are caused by blunt objects with relatively little subsequent tissue loss. We feel that it is necessary to establish a system for scoring the severity of high velocity missile injuries, in order to be able to predict morbidity and the risk of infection. Surgeons should be encouraged to devise a system for assessing the degree of tissue loss, which could become an objective measure of severity. The amount of fluid replacement needed might also serve as an objective parameter of the degree of severity of the injury.

Morbidity in severe war casualties can be reduced by preventing infection. Early surface decontamination and surgical debridement of the initial injury is essential in the prevention of early infections, and together with the initiation of penicillin therapy in all open wounds as soon after injury as possible, results in the virtual elimination of hemolytic streptococcal and clostridial infections.

The ability to predict the kind of injury likely to become infected in spite of these early prophylactic measures, may enable additional preventive measures to be initiated. We have identified at least three risk factors, and suggested that the early use of gentamicin and clindamycin in penetrating colonic injuries might prevent some of the infections associated with this particular risk factor. With most of the late-onset infections the problem is that of nosocomial infections in surgical patients, with nothing particularly peculiar to war wounds. Measures for the prevention of these infections are those generally recommended for the control of hospital-acquired infections. We have indicated that isolation procedures, barrier nursing and controlled antibiotic usage, prevented the further spread of antibiotic-resistant bacteria in at least one incident. These measures should never be neglected.

The same applies to other measures which we have not discussed, but which we do not regard as in any way less essential. Guidelines for infection control in intravenous therapy have recently been formulated,[8] and the importance of scrupulous care of indwelling urinary catheters including the use of closed drainage are accepted measures for preventing urinary tract infections.[10]

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Operative Management of Renovascular Hypertension

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From 1966 to 1975, 38 patients underwent 42 procedures for renovascular hypertension; 35 operations were aortorenal bypasses and 7 were nephrectomies. Forty-five per cent of the patients were cured, 43% were improved and 12% were unimproved. There were no operative deaths and only three late deaths. Two grafts occluded and 2 became stenotic, giving a graft complication rate of 12%.

Curability was best correlated with a short history of hypertension and a pathologic diagnosis of fibromuscular hyperplasia, but not with patient age. Most patients selected for surgery had elevated renal venous renin ratios, and of these 95% were cured or improved. Of those with normal renin ratios, 85% were still cured or improved. Postoperative aortography and peripheral renin measurements offered valuable information in predicting the ultimate response to surgery.

Preservation of renal function was a principal indication for surgery in 11 patients. In 8, azotemia was documented preoperatively. Hypertension was cured or improved in every case and 5 patients demonstrated a 10-50% reduction in BUN and creatinine following revascularization.

FIVE to 10% of the 30 million hypertensive patients in the United States have a potentially surgically curable form of the disease.[7,8] Stenotic lesions of the renal arteries constitute the predominant pathologic lesion found in these correctable forms of hypertension. This entity is now being recognized with increasing frequency at most centers treating the hypertensive patient, and a favorable response to surgical intervention has been demonstrated across a broad spectrum of the population.

This report concerns our experience in the operative management of renovascular hypertension at the Hospital of the University of Pennsylvania over the past 9 years. It confirms the generally favorable prognosis the vascular surgeon may offer his patient who has hypertension secondary to renal artery stenosis and emphasizes the concept that renal function may be preserved in the young hypertensive patient, and sometimes even improved by arterial bypass in those with renal parenchymal disease secondary to long standing ischemia.

Methods

The records of all patients undergoing renal revascularization procedures or nephrectomy for hypertension were reviewed. This report summarizes the results from June, 1966 to January, 1975. Thirty-eight patients underwent surgery and 4 were subsequently reoperated upon because of technical failure or progression of disease, making a total of 42 operations.

Selection of patients for surgery was based on rapid sequence intravenous pyelography, selective renal arteriography and peripheral and renal vein renin assays.

Renal vein renin samples were obtained preoperatively in 20 patients by selective catheterization of both renal veins. Peripheral renin levels were obtained from the inferior vena cava below the orifices of the renal veins. Renin concentrations were measured by the method of Gould et al.[11] which measures absolute concentrations of renin in Goldblatt units/ml plasma. Due to the variability in severity of hypertension, most patients were studied while still on antihypertensive medications. Usually they were on a combination of drugs which both stimulated and suppressed renin secretion so that the net phar-

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TABLE 1. *Distribution of Renal Vascular Hypertension.*

	Sex M	Sex F	Total	Caucasian	Negro	Average Age Yrs.
Arteriosclerotic	19	4	23	21	2	52.7
Fibromuscular Hyperplasia	3	12	15	14	1	26.9

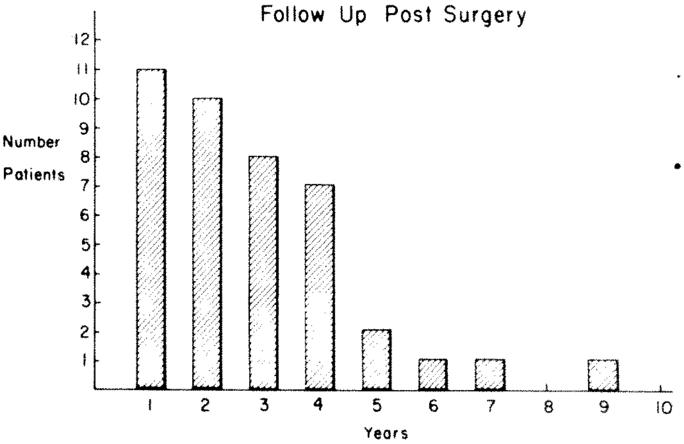

FIG. 1. Followup data post surgery for renal vascular hypertension.

macologic effect was difficult to determine. Only 5 of 20 patients were off all medication at the time of their study.

Due to the multitude of physiologic and pharmacologic factors capable of augmenting or suppressing the release of renin by the kidney, we have tended to emphasize the ratio of renin release by the diseased kidney (R_D) compared to the non-diseased kidney (R) during preoperative evaluation, rather than the individual renin concentrations alone. We have interpreted the ratio $R_D/R > 1.5$ as evidence of significant activation of the renin angiotensin mechanism by the diseased kidney. Likewise, we have interpreted a ratio between renin from a non-diseased kidney and the distal inferior vena cava R/IVC of less than 1 to be evidence of suppression of the renin angiotensin axis in the non-diseased kidney. From this model, one would expect patients who demonstrated an R_D/R ratio greater than 1.5 and R/IVC ratio of less than 1 to have the greatest probability of cure, while patients with the opposite condition can expect the poorest prognosis.

The technique of the aortorenal saphenous vein bypass is essentially that advocated by Foster.[8] A reversed, 5 cm segment of proximal saphenous vein, gently distended and irrigated, is anastomosed first to the aorta and then to the renal artery after Heparin (5,000 units) and Mannitol (50 mg) have been given. Both anastomoses are performed end-to-side with fine prolene suture and great care is taken to avoid kinking or twisting of the graft due to excessive length or poor positioning. Right-sided grafts have usually been brought retrocaval, and those on the left side are carried behind the renal vein.

In order to quantitate our results as objectively as possible, we have established 3 categories into which all patients have been stratified, based on their status at the most recent follow-up examination. We consider an individual "cured" if his blood pressure has fallen to the normal range (diastolic less than 90 mm Hg), and is off all anti-hypertensive medication. The "improved" patients require anti-hypertensives to maintain their blood pressure in the normal range or are more easily regulated on a less vigorous anti-hypertensive regimen than was required preoperatively. "Unimproved" patients are those whose blood pressure remains poorly controlled postoperatively, or those in whom no reduction in medication has been possible.

Results

Followup periods ranged from 2 to 103 months, with an average of 30 months (Fig. 1). There were no operative deaths, although 3 patients with advanced arteriosclerotic disease expired during the followup period, from 2 months to 3 years following surgery. Renal artery stenosis was secondary to arteriosclerosis in 23 patients and fibromuscular hyperplasia in 15 (Table 1). The majority of the arteriosclerotic patients were Caucasian middle age males, while the patients with fibromuscular hyperplasia tended to be young Caucasian females. This distribution of disease is entirely consistent with other published series.[4,8,9,17]

In 100% the arterial stenosis was demonstrated in either anteroposterior or special oblique projections on selective renal arteriograms. Twenty-nine per cent of patients who had normal IVP's were found to have significant renal artery stenosis. Nineteen patients (45%) were cured by surgery, 18 (43%) were improved, and 5 (12%) were unimproved. As demonstrated in Table 2, the cure-rate in patients with fibromuscular hyperplasia was superior to that in the arteriosclerotic patients, and 4 of the 5 unimproved patients came from the arteriosclerotic group. Nevertheless, 23 of 27 operations on patients with arteriosclerotic renal artery stenosis produced cure or improvement.

Table 3 confirms the generally accepted fact that the best results are seen in patients whose history of hyper-

TABLE 2. *Results of Surgery.*

	Cured	Improved	Unimproved
Arteriosclerotic	8	15	4
Fibromuscular Hyperplasia	11	3	1
Total	19 (45%)	18 (43%)	5 (12%)

TABLE 3. *Duration of Hypertension.*

	Total	Cured	Improved	Unimproved
<1 year	13	9 (69%)	4 (31%)	0
1 to 3 years	10	6 (60%)	3 (30%)	1 (10%)
>3 years	11	3 (27%)	6 (54%)	2 (18%)

TABLE 4. *Type of Operation.*

	Cured	Improved	Unimproved
Nephrectomy	2	4	1
Endarterectomy	1	1	1
Segmental resection	1	1	0
Vein graft			
Unilateral	12	10	2
Bilateral	0	1	0
Prosthetic graft			
Unilateral	2	1	1
Bilateral	1	0	0

tension is short. While 69% of patients with high blood pressure diagnosed less than 1 year prior to operation were cured (and the balance improved), only 27% of those with longstanding hypertension (greater than 3 years) could be cured of their disease, while 18% were unimproved. However, a long duration of hypertension should not be an absolute contraindication to surgery since 7 of our patients who had hypertension for 6 years or more were cured or improved.

The type of operation performed in each case was tailored to the individual needs of the patient. However, as the series evolved, the autogenous aortorenal saphenous vein bypass graft became the procedure of choice for uncomplicated renal artery stenosis, based on technical ease and superior overall clinical results. Revascularization procedures of several types were performed early in the series, as shown in Table 4, including endarterectomy with vein patch angioplasty and segmental resection of diseased arterial segments with primary end-to-end anastomosis. Bypass grafts of prosthetic woven dacron were generally performed in conjunction with distal aortic replacement for abdominal aortic aneurysms or aortoiliac occlusive disease. Nephrectomy has been reserved only for those cases where total absence of renal function, infarction, or end-stage parenchymal disease are demonstrated in the preoperative evaluation.

Table 4 catalogs clinical results based on the type of operation performed, and demonstrates the nearly uniform effectiveness (92%) of the saphenous vein bypass graft in curing or improving patients with renovascular hypertension. Two failures which occurred, 1 thrombosis and 1 stenosis, were results of technical misadventure. One patient subsequently benefited from nephrectomy.

The results in Table 5 indicate that when renin ratios (R_p/R) were greater than 1.5, 95% of patients were cured or improved. However, even in the 7 patients where R_p/R was less than 1.5, the cure and improved rate was still 85%. Consideration of the R/IVC ratio did not give any further predictive information. While it would appear that augmented renin release from the involved kidney was not a reliable indicator of potential surgical benefit, it is interesting to note that the majority of patients in our series (21/28) had an elevated renin ratio. In the postoperative period, 14 patients had peripheral renin levels drawn while they were supine, off all anti-hypertensive medication and on an ad-lib sodium diet. Those patients with renin levels of 1.2×10^{-4} Goldblatt units/ml or less (normal less than 2.0×10^{-4} Goldblatt units) had a greater than twofold likelihood of being cured of their hypertension than patients whose postoperative peripheral renin level was greater than 1.2×10^{-4} Goldblatt units (Table 6).

Postoperative arteriograms were obtained in 13 patients one week to three years postoperatively. Previous reports have demonstrated that technical errors committed at surgery are likely to be manifest early in the postoperative period as sustained hypertension due to anastomotic stenosis or graft thrombosis.[18] In our series, as shown in Table 6, there were 4 graft complications, 1 thrombosis and 3 stenoses, for a technical complication rate of 12%.

Twenty-nine per cent of our patients underwent renal revascularization procedures for the dual indication of correction of hypertension and preservation of renal function. This group includes those individuals with bilateral renal artery stenosis, patients with a hypoplastic non-functioning kidney and contralateral renal artery stenosis, young patients with tight (90%) stenosis for whom eventual renal deterioration seemed to be virtually certain even though hypertension could be controlled, and 1 patient (J.R.) with arterial stenosis and impaired renal function in a solitary kidney. Table 7 displays the results of bypass surgery in this group. All but 2 of the 11 patients had arteriosclerotic lesions and in every case hypertension was improved or cured. No patient has exhibited deterioration in renal function during the followup period; 3 patients in whom we intended to preserve normal renal function have remained normal; and 5 patients with impaired renal function preoperatively have demonstrated 10 to 50% reduction in serum BUN and creatinine values since surgery. One of these now has normal renal function.

TABLE 5. *Preoperative Renal Vein Renin Ratios.*

	Cured	Improved	Unimproved
$R_p/R > 1.5$	11	8	2
$R_p/R > 1.5$ and $R_p/IVC < 1.0$	5	3	0
$R_p/R < 1.5$	4	2	1
$R_p/R < 1.5$ and $R_p/IVC > 1.0$	4	1	1

TABLE 6. *Postoperative Studies.*

	Cured	Improved	Unimproved
Arteriogram			
Patent graft	5	3	1
Stenosis/occlusion	0	2	2
Peripheral renin			
>1.2	3	2	0
<1.2	7	2	0

TABLE 7. *Indications for Surgery.**

Patient, Age	Diagnosis	Hypertension	Renal Function Preop / Postop
1. C.B., 60	AS	Improved	Normal / Normal
2. T.C., 58	AS	Improved	Impaired / Improved
3. J.R., 52	AS	Improved	Impaired / Improved
4. J.K., 52	AS	Improved	Impaired / Improved
5. R.S., 33	FMH	Cured	Normal / Normal
6. E.L., 60	AS	Cured	Impaired / Normal
7. W.L., 57	AS	Improved	Impaired / Unchanged
8. B.M., 50	AS	Improved	Impaired / Unchanged
9. C.M., 49	AS	Improved	Impaired / Unchanged
10. L.F., 66	AS	Improved	Impaired / Improved
11. L.K., 52	FMH	Improved	Normal / Normal

*Hypertension alone—31; Hypertension and preservation of renal function—11.

Discussion

In 1969, two sources advocated that, in general, patients over age 45 should not undergo operative correction of renal artery stenosis, since the risks were too great, and the potential benefits too small.[5,16] Furthermore, with operative mortalities ranging from 5.4% to 14%, and failure rates as high as 20% in one combined series, enthusiasm for renal artery bypass surgery was understandably diminished.[2,8,17] However, recent reports from Ernst,[6] together with our own results, have tended to contradict such earlier data. No operative deaths occurred in the followup period, while 88% were cured or improved despite the fact that 57% were over age 45.

The aortorenal saphenous vein bypass graft appears to be withstanding the test of time, since the majority of these grafts have remained patent and have produced therapeutic benefit over extended followup periods. Typical varieties of graft complications have been described, including aneurysmal dilatation, stenosis and thrombosis.[18] When these are due to technical failure, they generally appear within two weeks of operation, and we have seen a few instances of this. We agree with Kaufman[14] that prosthetic grafts are a reasonable alternative to a vein graft, particularly since graft length is short and flows are usually high. However, we have generally reserved their use for renal artery bypass combined with distal aortic replacement, and would only resort to it if a satisfactory vein were unavailable. Nephrectomy should be offered only to patients with confirmed absence of renal function and should be avoided as a first line of therapy in the pediatric and young adult age groups.[10]

Optimal criteria for the selection of patients for surgery are still unclear. The value and limitations of the rapid sequence intravenous pyelogram to establish laterality and identify unilateral impairment of renal function are not well appreciated. While 71% of our patients had abnormal radiographic signs on IVP, all of those who did not were still cured or improved by surgery. This emphasizes the need for arteriography when the IVP is normal if the clinical situation warrants. Arteriography remains the definitive diagnostic procedure when performed correctly. Dean et al.[3] have emphasized the deceptive patterns of renal artery stenosis and recommended more precise methods of identifying these lesions by arteriography, including the use of oblique projections to locate stenosis lying in the anteroposterior plane.

Several groups have advocated precise and controlled collection of selective renal vein and peripheral renin samples and emphasized the value of renin ratios to facilitate patient selection and index predictability of surgical benefit.[1,6,12,19,20] However, general agreement does not exist on the critical renal vein renin ratios as an indicator of laterality of disease. Estimates range from 1.4 to 2.0, and as shown in Table 8, the results of several series reported over the past decade have been equivocal at

TABLE 8. *Preoperative Renal Vein Renins and Surgical Results.*

		Renin Ratio Elevated Patients	Renin Ratio Elevated % Improved	Renin Ratio Normal Patients	Renin Ratio Normal % Improved
Judson[13]	1965	16	100	15	0
Michelakis[15]	1967	18	90	3	33
Gunnells[12]	1969	19	79	6	17
Foster[9]	1969	12	92	6	83
Foster[8]	1973	39	100*	4	100
Stockigt[19]	1972	32	90	9	55
Ernst[7]	1972	30	100*	7	100
McCombs Present Series	1975	20	95	7	85

*Selected series of patients all of whom were cured.

best in identifying unilateral activation of the renin-angiotensin system as the principal etiologic factor in renovascular hypertension. Our own results also cast doubt on the absolute reliability of elevated renin ratios in predicting a favorable response to surgery, since 95% of patients with elevated renin ratios as well as 85% of patients with normal renin ratios were benefited by revascularization. The data cited by Foster,[8,9] Stockigt,[19] and Ernst[7] are not dramatically different from ours. Thus the evidence seems to suggest that renal vein renin ratios are only useful in a relative, rather than absolute, sense in patient selection, and that interpretation should be tempered with the realization that many hypertensive patients with renal artery stenosis but poor lateralization of renin release may nevertheless be cured or improved by surgery.

Postoperatively, these patients deserve close followup attention. While one might be reluctant to subject a patient who is doing well to aortography, our experience and others' has been that, with low attendant risk, valuable prognostic information can be gained, since signs of trouble are likely to appear early by x-ray.[18] Peripheral renin levels, too, have shown some correlation to the ultimate response of hypertension to surgery. Vaughan's data[20] like our own, suggest that a low value in the early postoperative period, uninfluenced by erect posture, anti-hypertensive medication, or dietary restriction, is a favorable sign.

Other investigators have suggested the value of renal artery bypass for preservation of renal function in specific cases,[7,8] but we have not seen this concept demonstrated as clearly as in the present series. Even in risky patients with advancing azotemia, secondary to chronic renal ischemia, no patient exhibited progression of renal failure postoperatively, and 5 demonstrated definite regression toward normal. Renal revascularization thus extended dual benefit to this group.

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Mesenteric Leaf Repair of Pelvic Defects Following Exenterative Operations

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Perineal enterocutaneous fistula and hernia are unique complications of radical pelvic exenterative operations. A technique for management of these complications is presented. A vascularized segment of small bowel mesentery is interposed as a peritoneum covered pelvic "lid" to separate the abdominal contents from the pelvic defect.

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PROLAPSE of the small intestine through the perineum and perineal enterocutaneous fistula are two complications uniquely associated with partial or complete removal of the pelvic organs.

Prolapse of small intestine occurs in two clinically distinct manners. If the perineal skin is closed the herniating intestine is protected by an epithelial surface. These presensations often can be managed with supportive clothing. On the other hand, if the perineum is open the intestine is subject to drying, direct trauma, and infection. These prolapses require surgical correction.

Enteroperineal fistulae after partial or total pelvic exenteration have several features in common. After operation the small intestine descends into the deperitonealized pelvic cavity and becomes bound together and to the pelvic walls by adhesions. Partial or complete small bowel obstruction frequently precedes the development of fistula.[3] At laparotomy the fistula is often partially lined with mucosa which has grown out of the intestinal defect. Spontaneous closure of these fistulae is infrequent.[3,4,6]

The pathologic features of small intestinal prolapse and enteroperineal fistula have been recognized by others, and multiple techniques have been advocated to prevent their development. Brunschwig, in his original description of the pelvic exenteration procedure, advocated packing the pelvic defect with gauze to prevent descent of the small intestine into the true pelvis in the immediate postoperative period.[1] The pack is left in place for 7 to 10 days with the hope that the small intestine would become adhesed to itself and the surrounding structures in the

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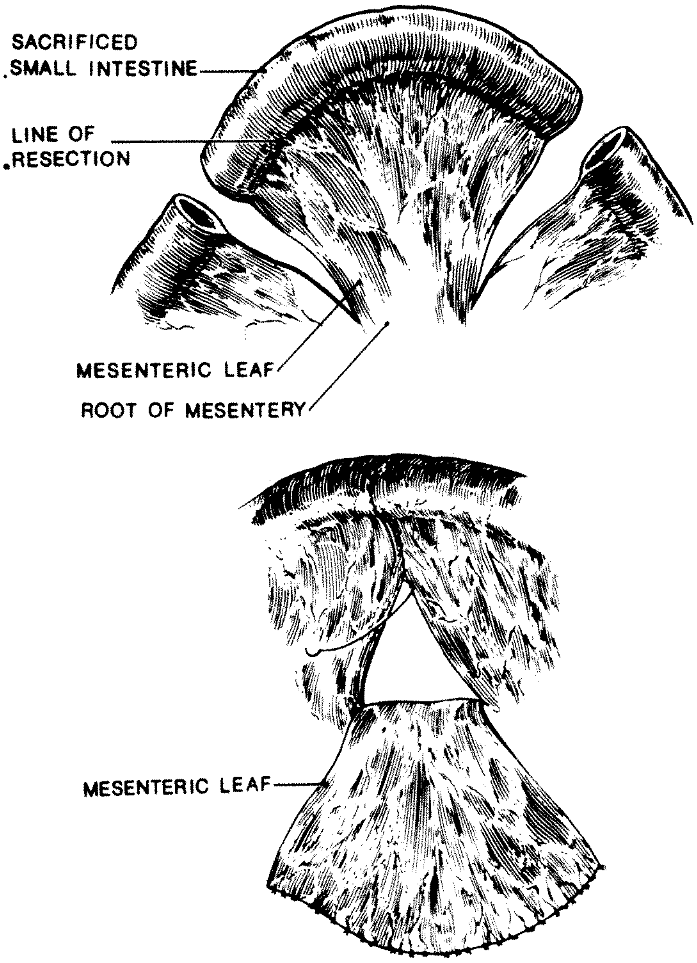

FIG. 1. Creation of the mesenteric leaf.

abdominal cavity. Schmitz et al. suture a wire mesh diaphragm to the true pelvic brim to prevent descent of the small intestine into the pelvis.[7] Others have applied this principle of a pelvic "lid" using different materials. Green and Patterson advocated a diaphragm of reconstituted collagen, Wheeless et al. used marlex, and Foley and Fetherston used teflon.[5,8,4] Buchsbaum and White formed a pouch for the small intestine by suturing the free margin of the greater omentum to the posterior peritoneal cavity inferior to the intestine.[2] Morley and Lindenauer described a second procedure using living tissue: They created a pedicle of parietal peritoneum dissected from the anterior abdominal wall to resurface the pelvic defect.[6] In both of these procedures the small intestine is separated from the pelvic defect by a diaphragm of living tissue.

In this paper we describe a method that we have used successfully in the treatment of two patients, one with prolapse and one with fistula. Our technique incorporates the principles described above. A segment of small bowel mesentery is used to form a pelvic "lid" of living tissue that separates the intestine from the pelvic defect.

Method

An appropriate portion of mesentery of small intestine is identified (Fig. 1). Approximately 20 to 25 cm of intestine is carefully removed to form a pie-shaped wedge of mesentery (Fig. 1). It is critical that the mesentery be transected as near as possible to the bowel wall, to achieve maximum leaf area and maximum expansibility of leaf edge. The continuity of the intestine is restored anterior to the leaf (Fig. 1). The leaf is attached to the margin of the true pelvis. We have found it helpful to place the sutures in the entire circumference of the pelvic inlet before any are passed through the leaf. Next the leaf is positioned and all sutures are passed through its edges before any are tied. Figures 2 and 3 depict the final position of the mesenteric leaf and its relationship to the pelvis. The pelvic cavity inferior to the leaf is packed with gauze to provide support for the leaf and drainage in the immediate postoperative period. The small intestine is positioned above the mesenteric diaphragm and the abdomen is closed. The two patients we have treated were kept recumbent for 10 days after operation in a further effort to prevent separation of the leaf from the pelvis.

Case Reports

Case 1: E. R., a 54-year-old Caucasian woman, underwent total pelvic exenteration for advanced carcinoma of the cervix in 1967. Her postoperative convalescence was uncomplicated. The margins of the specimen and all lymph nodes were negative for tumor. In 1968 she developed the first of five separate enteroperineal fistulae. Each was treated unsuccessfully by attempts at operative closure. The last fistula was repaired in August 1973 using the mesenteric leaf technique. She has remained well since that time without evidence of refistulization.

Case 2: H. G., a 41-year-old Caucasian woman had Stage I squamous carcinoma of the cervix diagnosed in 1966 and was treated with radiation therapy. In 1973 Pap smear demonstrated squamous cell carcinoma. There was an ulcerating lesion in the anterior vaginal wall which invaded the base of the bladder. This tumor was either a second primary or a recurrence of the original cervical carcinoma. She was treated by

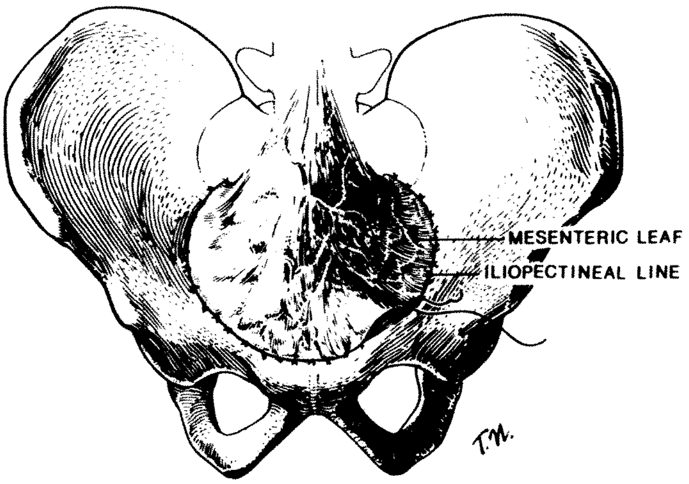

FIG. 2. Anterior view of the mesenteric leaf showing its attachment to the pelvic brim.

anterior pelvic exenteration. Her postoperative convalescence was uncomplicated. The margins of the specimen and all lymph nodes were free of tumor. Three months postoperatively she developed progressive prolapse of small intestine through the anterior perineal defect with exposure of bowel serosa. At laparotomy small intestine was detached from the pelvic walls and elevated into the abdominal cavity and the pelvic defect was closed with a mesenteric leaf. At present the serosal surface of the leaf can be seen through the exenteration defect. The hernia has not recurred thus far 18 months after the repair.

Discussion

The method of repair described takes into consideration two important principles. First, it partitions the abdominal from the pelvic cavity and the denuded pelvic walls. Second, the separation is accomplished with living tissue covered with peritoneum on both surfaces.

A disadvantage of this procedure is the sacrifice of a segment of small intestine. In our first case the segment excised was involved in the fistula and sacrifice was inevitable. In our second patient, the possible gains with the procedure were weighed against the morbidity of excision of normal small intestine and was considered warranted to prevent future herniation and subsequent complications.

We feel it is important to pack the pelvic cavity with gauze and to keep the patient supine for approximately 10 days after surgery to allow attachment of the mesenteric leaf to the pelvic walls before the weight of the small intestine is placed upon it. In both of our cases, postoperatively the small intestine slowly descended into the pelvis. We feel that descent of the intestine at a slow rate is not as detrimental as immediate descent. With this repair technique the small intestine rests upon a surface covered with peritoneum. This should in part circumvent the problems associated with adhesions to the denuded pelvis and immobilization of the intestine. Our repair obviates the placement of foreign material in an area which is inevitably infected in the postoperative period.

The full applicability of this technique has not been explored. At present we have used it in only two patients. The technique may be indicated as an elective procedure after pelvic exenterations when in the judgment of the operator there is a high likelihood of the development of perineal hernia or enteroperineal fistula.

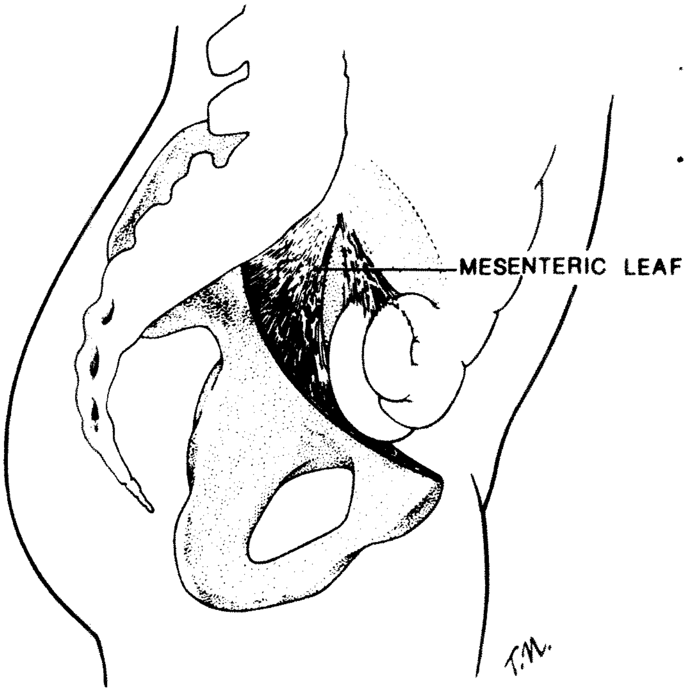

FIG. 3. Lateral view of the mesenteric leaf showing its relation to the pelvis and the abdominal contents.

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Wound Infections in Renal Transplant Wounds:

Pathogenetic and Prognostic Factors

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The factors contributing to transplant wound infection, as well as those determining its outcome, have been reviewed in 27 transplant patients with wound infection. Unrelated cadaver kidneys, diabetes, urinary fistulas and wound hematomas are all factors predisposing to wound infection. Overall incidence of wound infection in this series was 6.1% (27/439). When infections secondary to known preventable causes (i.e. hematomas and fistulas) were excluded, the incidence of wound infection was only 1.6%. Furthermore, if diabetics and retransplanted patients were excluded, the incidence of wound infection in non-diabetic patients who had their first transplant was only 0.7%. Perinephric infections are much more serious and carry a worse prognosis than superficial infections. Overall mortality of wound infections was 30% (8/27), most deaths being caused by sepsis from deep infection. Only three patients (11%) healed their wounds and saved their kidneys, whereas the rest of the survivors (15/18) healed their wounds but lost their kidneys. It is emphasized that prevention of hematomas and urinary fistulas is the most important measure in the prevention of transplant wound infection.

SURGICAL WOUND INFECTION has been a subject of considerable clinical and experimental study.[4,6,18] Transplant wound infections deserve particular attention, because of the special conditions associated with them and because of the serious consequences that wound infections may have for these patients. These special conditions are: 1) the uremic state of the patient at the time of surgery and sometimes in the immediate post-transplant period; 2) the presence of a "foreign" organ in the surgical wound; and 3) the increased susceptibility of heavily immuno-suppressed patients to infection.

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Previous studies of transplant-wound infections reported an incidence ranging from 1.8% to 56%.[5,16,21] The purpose of this study is a detailed analysis of all causes and predisposing conditions leading to wound infection. An understanding of these conditions should lead to a decrease in the incidence of transplant-wound infections and the attending morbidity and mortality.

Materials and Methods

A retrospective analysis of the transplant-wound infections seen at the University of Minnesota Hospitals from August 1967 to July 1973 was made. During this period, 439 kidneys were transplanted to 378 patients; of these, 378 were first transplants, 51 second transplants, 7 third transplants and 3 fourth transplants. Two hundred and fifty-seven out of 439 kidneys were donated by living volunteer relatives and 182/439 were of cadaver origin. A wound was considered infected when there was pus in the wound and bacterial cultures were positive. Serous discharge or urinary leaks with negative bacterial cultures were not considered infected unless repeated cultures proved infection to be present.

The operative technique and immunosuppressive regimen used at the University of Minnesota has been described in detail elsewhere.[22] In adults, the kidney transplants were placed retroperitoneally in one of the iliac fossae through lateral lower quadrant incisions, whereas in children weighing less than 20 kg they were placed intra-abdominally through midline abdominal inci-

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TABLE 1. *Age Distribution of Transplant Wound Infections*

Age (Years)	RATIO # Infections/ # Transplants	RATIO # Diabetics/ # Transplants
0-10	*1/47 (2.1%)*	0/47 (0%
11-20	4/80 (5%)	0/80 (0%)
21-30	8/85 (9.4%)	23/85 (27%)
31-40	9/99 (9%)	33/99 (33.3%
41-50	4/74 (5.4%)	8/74 (10.8%)
51-60	1/49 (2%)	1/49 (2%)
61-70	0/5 (0%)	0/5 (0%)
Total	27/439 (6.1%)	65/439 (14.5%)

sions. All the wounds were irrigated with neomycin or neomycin-bacitracin solutions during the procedure, and some of the wounds were drained with a hemovac drain for 24-36 hours. Skin sutures were routinely removed on the tenth postoperative day. All patients were treated with prophylactic semisynthetic penicillin, starting the day before surgery and continuing for 10 days after operation.

Results

There were 27 wound infections in 439 kidney transplants carried out since August of 1967—an incidence of 6.1%. Eleven (2.5%) were subcutaneous infections, but 16 (3.6%) involved the perinephric tissues.

Effect of recipient age on incidence of wound infection

Table 1 analyzes the distribution of wound infections in patients of various ages. The highest incidence of infection was in the third and fourth decades, 9.6% and 9% respectively, with a lower incidence in younger and older patients. This higher incidence in the third and fourth decades corresponds mainly to the higher incidence of infections in young adults with juvenile insulin dependent diabetes (Tables 1 and 2).

Diabetic versus non-diabetic patients

Of the total series of transplanted patients, 65 (14.5%) were diabetics and 374 were non-diabetics. The incidence of infection in the diabetic group was twice as high as in the non-diabetic group. Peri-nephric infections were also more common in the diabetic patients. Conversely, almost half of the infections in non-diabetic patients were superficial (Table 2).

TABLE 2. *Incidence of Infection in Diabetic and Non-Diabetic Patients**

	# Patients	Total Infections	Incidence of Perinephric Infection
Diabetic patients	65	7/65 (10.8%)	5/65 (7.7%)
Non-Diabetic patients	374	20/374 (5.3%)	11/374 (2.9%)

*Chi squared analysis yields $P \leq 0.05$ for this table.

TABLE 3. *Incidence of Infection in Cadaver and Related Kidney Recipients**

	# patients	Incidence of Infection	Incidence of perinephric infections
Cadaver Kidney Recipients	182	18/182 (9.9%)	12/182 (6.6%)
Related Kidney Recipients	257	9/257 (3.5%)	4/257 (1.5%)

*Chi squared analysis yields $P \leq 0.005$ for this table.

Cadaver versus related kidney recipients

Table 3 demonstrates that recipients of cadaver kidneys had almost three times the incidence of wound infections when compared with recipients of related kidneys. Peri-nephric infections were also more common in recipients of cadaver kidneys (Table 3).

Influence of pre-transplant organ perfusion on wound infection

Of the 182 cadaver kidneys, 107 were perfused on the Mox-100 preservation machine for variable periods of time. Perfusion of the kidney did not predispose to wound infection since the incidence of infection in the perfused cadaver kidneys was 9/107 (8.4%) and in the non-perfused group was 9/75 (12%). The cryoprecipitated plasma perfusate was cultured during and after all perfusions. Perfusate bacterial cultures were positive in 25/107 cases. Staphylococcus was cultured in 18 cases, pseudomonas in four, unidentifiable gram negative rods in two, and β-streptococcus in one case. There was no correlation between the types of bacteria found in positive perfusate cultures and that found in the wound infection, although three kidneys with staphylococcus in the perfusate later developed wound infection with gram negative organisms. Also the length of perfusion did not predispose to contamination of perfusate. On the contrary, 20 of the 25 perfusates which became contaminated did so in the first 6 hours of perfusion. The length of perfusion was also not a contributing factor to the incidence of infection (Table 4). The mean perfusion time of the non-infected group was 19.5 hours and of the infected group 18.3 hours.

TABLE 4. *Relation of Length of Preservation to Incidence of Wound Infection in 107 Perfusion-Preserved Cadaver Kidneys**

Total Hours of Perfusion	Incidence of Wound Infection
12	1/23 (4.3%)
13-24	7/62 (11%)
25-36	1/22 (4.5%)

*Chi squared analysis is not significant ($P \geq 0.05$)

TABLE 5. *Multiple Factors Predisposing to Wound Infection: Deep Infections*

Patient	Age, Sex	Transplant #	Juvenile Diabetes	Cadaver Donor	ATN	Hematoma	Urinary Fistula
1	34, M	1	+	–	+	+	+
2	34, M	2	+	+	+	+	+
3	29, M	1	+	+	–	+	+
4	40, M	1	+	+	–	–	+
5	29, F	1	+	+	–	–	+
6	24, F	1	–	+	+	–	+
7	20, M	1	–	+	+	+	–
8	35, M	1	–	+	+	+	–
9	56, F	1	–	+	+	+	–
10	39, M	2	–	+	+	+	+
11	24, F	1	–	+	–	–	+
12	25, F	1	–	+	+	+	–
13	45, M	1	–	+	+	–	+
14	11, F	1	–	–	+	+	+
15	25, M	1	–	–	+	+	–
16	19, M	1	–	–	+	–	+

Effect of wound hematomas on the incidence of transplant wound infection:

In the whole transplant series, there were 30 wounds which required re-exploration in the immediate posttransplant period because of bleeding, an incidence of 7%. The distribution of hematomas in the recipients of living related kidneys was 14/257 (5.4%) and cadaver kidneys was 16/182 (8.8%). Of these 30, 14 became infected (46%). Ten of the infected hematomas were associated with perinephric infections and 4 with superficial infections. Nine of 10 deep wound infections which followed wound bleeding were associated with renal malfunction which required at least one posttransplant dialysis. Thus, almost half of the 27 wound infections in the entire series were related to excessive bleeding into the wound which required re-exploration and was associated with early renal malfunction.

Effect of urinary fistulas on the incidence of transplant wound infections:

In the entire series there were 17 urinary fistulas, an incidence of 3.9%. Five of these never became infected. Of the 12 that became infected, 11 were associated with perinephric abscesses. Significantly, 5/67 (7.7%) diabetics developed urinary fistulas and all became infected. 12/374 (3.2%) non-diabetic patients developed urinary fistulas and 7/12 became infected. Ten of the patients with wound infection after urinary fistulas had simultaneous urinary tract infection, and bacterial cultures were identical in both wounds and urine. Interestingly, 7 other patients with wound infections had identical cultures in wound and urine without a urinary fistula.

Of the total of 27 infections 11/27 were superficial and 16/27 were perinephric. Of the 16 deep infections all were associated with either urinary leak or perinephric hematoma (Table 5). Of the 11 superficial infections only 4 were associated with a wound hematoma or urinary fistula. (Table 6)

Effect of posttransplant renal function on the incidence of wound infection

Of 439 transplant patients, 70 (16%) had acute tubular necrosis (ATN) as defined by a need for at least one hemodialysis in the posttransplant period. Forty-four of those were recipients of cadaver kidneys and 26 recipients of related kidneys. Eighteen out of 70 (25.7%) of the patients who required dialysis in the posttransplant period became infected. In contrast, of the 369 patients who did not require dialysis after transplantation, only 9/369 (2.4%) became infected ($P \leq 0.005$).

It is likely that ATN itself does not predispose to wound infection and that other factors are at work. Whereas 26 patients with related transplants required posttransplant hemodialysis, only three non-diabetic patients (patients 14, 15, and 16, Table 5) developed deep wound infections. Two of these had intestinal fistulas, (patients 14 and 16), one from an attempted transplant to an ileal loop and one due to a known technical error during transplant when bowel was accidentally entered. Only one patient without diabetes or intestinal fistula developed wound infection after requiring hemodialysis (patient 15). There was known bleeding into the wound on the night of transplantation and this hematoma was not evacuated. Thus, ATN by itself cannot be a cause of deep wound infection in patients without complications. In fact, Tables 5 and 6 demonstrate that multiple factors are present in most patients with wound infections. No patient with ATN developed wound infection without some other predisposing cause. Table 6 similarly demonstrates only one patient who developed a superficial wound infection in whom ATN might have been the only

TABLE 6. *Multiple Factors Predisposing to Wound Infection: Superficial Infections*

Patient	Age, Sex	Transplant #	Juvenile Diabetes	Cadaver Donor	ATN	Hematoma	Urinary Fistula
17	35, M	1	+	–	–	–	–
18	29, F	1	+	+	–	–	–
19	1, M	2	–	+	–	–	–
20	31, M	1	–	+	–	–	–
21	30, F	3	–	+	+	–	–
22	40, F	1	–	+	–	+	–
23	47, M	1	–	+	+	–	–
24	41, F	1	–	–	+	+	–
25	20, F	1	–	–	+	–	–
26	49, M	1	–	–	–	+	+
27	35, F	1	–	–	+	+	–

predisposing cause (Patient 25). As will be seen below, renal malfunction in early posttransplant period due to accumulation of hematoma within the wound seems to be the combination which predisposes to wound infection rather than ATN alone.

Effect of repeated transplantation on the incidence of wound infections:

The incidence of wound infection in first transplants was 6% (23/378), in the second transplants, 6% (3/51), and in subsequent transplants, 10% (1/10). It can be seen that the incidence of wound infection in first and subsequent transplants is approximately the same.

Bacteriology of wound infections:

Gram negative rods accounted for the majority of wound infections. Enterococcus and staphylococcus were the only gram positive cocci recovered from infected wounds. The infecting organisms in the 27 wound infections are listed in Table 7. Of the 27 patients with wound infections, 17 had simultaneous bacteriuria usually with the same organisms (Table 7).

Complications of wound infection: There were three main complications resulting from wound infection: Septicemia occurred in 10/27 (37%) cases development of mycotic aneurysm of the iliac vessels or the aorta in 7/27 (26%) cases, and transplant nephrectomy became necessary in 15/27 (55%) cases. Each of these three categories will be considered separately.

Septicemia: Of the 10 cases, three were caused by pseudomonas, three by enterococcus, two by *E. coli*, one by Klebsiella, and one by bacteroides. Pseudomonas was a particularly virulent organism in that it caused septicemia in 60% of the cases in which it was cultured from wounds whereas enterococcus septicemia occurred in 25% of these cases in which the organism was cultured, and for *E. coli* the incidence of septicemia was only 14%. There was no difference in incidence of systemic sepsis between diabetics and non-diabetics. Cadaver kidney recipients accounted for 8 of the 10 cases of septicemia. Half of the 10 cases survived and the other half died as a result of sepsis.

Mycotic aneurysms of the iliac vessels occurred in 6 cases of 16 deep wound infections and one of these later developed a mycotic aneurysm of the aorta. Of these, 4 were diabetics, representing in incidence of 80% of the deep infections in diabetic patients; 3/11 deep infections in non-diabetic patients developed mycotic aneurysms. None of the patients with subcutaneous infections developed mycotic aneurysms. Three of the aneurysms necessitated transplant nephrectomy at the time of exploration; two aneurysms developed after transplant nephrectomy was done for perinephric abscess. One kidney was saved and retained good function after ligation of the involved external iliac artery. Another kidney retained excellent function after resection of the aneurysm with axillofemoral by-pass graft with retrograde perfusion of the kidney. There was only one death as a result of the aneurysm. This occurred as a result of later rupture of the aortic stump in the case described above. The rest of the patients survived the rupture of their aneurysms following successful ligation of the involved artery.

TABLE 7. *Bacteriology of 27 Wound and 17 Simultaneous Urinary Tract Infections*

	No. of wound infections with organisms*	No. of urine cultures with organisms	No. of organisms in common
E. coli	14/27	9	9
Enterococcus	12/27	5	5
Candida albicans	11/27	5	5
Staphylococcus	5/27	0	0
Pseudomonas	5/27	3	3
Klebsiella	3/27	4	3
Proteus	2/27	0	0
Bacteroides	2/27	2	2
Citrobacter diversus	2/27	1	1

*Mixed infections account for a greater number of types of organis cultured than number of wound infections.

Transplant Nephrectomy: Transplant nephrectomy was done in 15 cases. Of these, 12 were associated with perinephric abscess and three were done because of superficial wound infection associated with severe rejection. Thus, 12/16 of the patients with deep perinephric infections lost their kidney as a direct result of the infection.

Outcome of Wound Infections: The overall mortality of wound infection was 29.6% (8/27). Five deaths were the result of septicemia complicating deep wound infection. One died later of a ruptured aortic mycotic aneurysm, one died of a myocardial infarction and one baby with superficial infection died of pneumonia. Eighteen of 27 wounds healed completely but only three healed with the transplant intact. All the rest (15/18) underwent nephrectomy.

Of patients who lost kidneys but survived wound infections, 4 were transplanted again. Two out of four had second wound infections, and both died of sepsis at some time after second transplant.

Discussion

Infection is frequently a life-threatening complication in the immunosuppressed transplant recipient and remains the most common cause of death in these patients.[24] Previous reports pointed out that infections of transplant wounds are common[5,16,21] and predisposing factors are not difficult to find. Uremia, immunosuppressive drugs, bacteremia during hemodialysis due to defects in the dialysis membrane, chronically infected hemodialysis catheters, the contamination of wounds with urine, cadaver kidneys from unknown or poorly defined sources, pre-existing infections of anuric bladders, and diabetes all appear to predispose to infection. Though prophylactic antibiotics can eliminate gram positive organisms,[14] they have not proven effective against gram negative organisms.

Immunosuppression seriously impairs the defense mechanisms of transplant patients. Steroids decrease the rate of healing of wounds[9,12] and make them more vulnerable to infection.[26] Azathioprine also causes leukopenia nd impairs the immune response.[27] Uremia is also as-ciated with poor wound healing and wound dehis-ce[19] and increased risk of infection.[15] In addition, nic patients have a bleeding diathesis[11,13] and this may to hematoma formation, particularly after dialysis,[10] subsequent infection.

overall incidence of wound infection in this series .1%. If, however, those secondary to hematoma or y fistula are excluded (Tables 5 and 6) as being due hnical error and probably entirely preventable then cidence of wound infection in the uncomplicated d is only 1.6% (7/439). Furthermore, all 7 patients uperficial infections (17, 18, 19, 20, 21, 23, and 25). Two of these were diabetics and 5 were recipients of cadaver kidneys. In two patients, infection followed second and third transplants respectively and one infection followed re-exploration of the wound for correction of arterial kink (Patient 25). If diabetics and retransplanted patients were thus excluded, the incidence of wound infection in non-diabetic patients who had their first transplant was only 0.7% (3/439), and all three infections were superficial. The 1.6% infection rate of uncomplicated transplant wounds was lower than the 1.81% rate of infection of clean general surgical procedures[4,6] and definitely lower than the 4.7% rate of infection in herniorraphy and 14.3% infection rate in breast surgery.[4]

The higher incidence of wound infection in cadaver kidney recipients has been observed by others.[16] This may be due to higher doses of immunosuppressants and possible kidney contamination during preservation. Although the 25 positive perfusate cultures did not correlate with clinical infections, they, however, indicate that contamination does take place.

Diabetes in itself is known to predispose to infection.[2,7,17] Furthermore, the incidence of urinary fistulas in diabetics is much higher than in non-diabetics (7.7% vs. 3.2%)[23] and when this occurs, wound infection almost inevitably follows. The severity of infection depends on the number of factors involved in its development. All deep infections were associated with either hematoma or urinary fistula or both (Table 5), whereas of the superficial infections only 4 were associated with hematomas and only one with urinary fistula. Also 12/16 of deep infections were in cadaver kidney recipients but of the superficial infections only 6/11 were of cadaver recipients. Also 5/16 of deep infections were in diabetics and only 2/11 of superficial infections were in diabetics. Thus, the more frequent presence of predisposing factors such as diabetes, cadaver origin of kidneys, hematomas and urinary leaks leads to the more serious deep infections.

The two surgical complications which predispose to all deep infections, i.e. hematomas and urinary fistulas, are potentially preventable by good surgical technique. In addition to surgical error, hematomas may result from the inherent bleeding diathesis of uremic patients,[11,13] or posttransplant renal malfunction which require anticoagulation during hemodialysis.[10] The seriousness of hematomas as predisposing causes of infection and the role of local hematin compotents in the pathogenesis of infection has been also reported by others.[25]

The prevention of hematoma in transplant wound is of paramount importance. Wound hemostasis must be meticulous. Particularly in cadaver kidneys, which are usually hastily harvested, attention to hemostasis must be extreme. Small bleeding points in the kidney capsule and around the renal pelvis must be controlled after transplantation. This problem may be complicated since renal flow to the ischemic kidney may be delayed so that small vascular defects might not be noted. Recipients may also have recently received anticoagulants to maintain patent shunts or fistulas, or may have required emergency pretransplant dialysis; transplantation must be delayed until *in vitro* coagulation parameters have returned to normal.

We are in agreement with other investigators[21] who have found that the consequences of wound infection are disastrous for both the kidney and the patients. Superficial infections could be drained, but deep infections led to the loss of kidney in 75% of the cases. Mycotic aneurysms occurred in 37.5% and septicemia in 62.5% of deep wound infections. Half of the patients with septicemia died. The remainder of the patients had open wounds requiring prolonged hospitalization. Of 57 cases of septicemia in transplant patients reported by Anderson,[1] 10 cases were due to wound infection. Mycotic aneurysms are a serious complication and open infected wounds should be assessed frequently for early detection of this potentially lethal condition.

Treatment of transplant wound infection follows the general surgical principles of drainage and irrigation. If the presence of the graft prevents adequate drainage, as it frequently does, transplant nephrectomy should be performed. Appropriate antibiotics should be administered but certain organisms like pseudomonas present serious and potentially lethal problems regardless of the antibiotics chosen.

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Effect of Intravascular Cellular Aggregate Dissolution in Postoperative Patients

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It was the purpose of this study to confirm whether the increase in packed cell (PC) viscosity that occurs in humans after elective surgery is accompanied by a decrease in total body O_2 consumption as previously noted in animals, and further to define the effect of resolution of intravascular cellular aggregates (ICA) on these parameters. Thirty nine patients were studied. Total body O_2 consumption was 76% of normal 6 hours postop, 81% of normal 24 hours postop and 87% of normal 48 hours postop. Twenty four hours after operation PC viscosity had increased markedly. Saline infusion had no significant effect on total body O_2 consumption or PC viscosity, either pre- or postop, but WB viscosity decreased linearly in proportion to the drop in hematocrit. Resolution of ICA by dextran-40 infusion was associated with return of total body O_2 consumption and PC viscosity to normal; a decrease in WB viscosity was disproportionately greater than would have been seen had the decrease been due solely to the drop in hematocrit. It is concluded that in humans surgical trauma causes an increase in PC viscosity and microcirculatory impairment as evidenced by a decrease in total body O_2 consumption. Resolution of ICA by dextran-40 infusion reverses these detrimental changes.

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TRAUMATIC TISSUE INJURY in animals and humans causes intravascular cellular aggregation.[1,5,11,12,16,17,19] Moderate to severe aggregation can cause stasis or total blockage of capillaries. This phenomenon can readily be studied in vivo in the small blood vessels of the bulbar conjunctive.[12,18,19] When a significant number of vessels are blocked, tissue oxygenation is endangered.[2,3] In animals severe operations cause intravascular cellular aggregation (ICA), increased packed cell viscosity and decreased O_2 consumption.[17,18] Resolution of ICA by infusion of dextran-40 leads to reversal of these detrimental changes.

It has been demonstrated that an increase in PC viscosity also occurs after operation in humans.[22] It was the purpose of this study to confirm whether the increased PC viscosity that occurs in humans after elective surgery is accompanied by a decrease in total body O_2 consumption as previously noted in animals and further to define the effect of resolution of ICA on these parameters.

Methods

Patients were studied before and after undergoing elective operations of Scales 3 to 6 on Moore's scale of operative severity.[25] All received routine therapy as indicated and were divided into three study groups.

Group I. Control group (9 patients). Venous blood and expired respiratory gas samples were taken 24 hours preoperatively and 6, 24 and 48 hours after operation. Previous research demonstrated that such patients will develop increases in PC viscosities after operation.[22] This group was studied to confirm whether such changes are accompanied by a decrease in total body O_2 consumption.

Group II Infusion control group. Venous blood and expired respiratory gas samples were taken only in the preoperative period both before and after infusion.

A. Saline Infusion (5 patients). These patients were given 1000 cc normal saline intravenously as a rapid infusion over 15 minutes.

B. Dextran-40 Infusion (7 patients). These patients were given 500 cc 10% dextran-40 in normal saline intravenously over 30 minutes.

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TABLE 1. *Oxygen Consumption in Patients Infused Before or After Operation (ml/min.)*

	Preoperative			Postoperative		
				6 Hrs	24 Hrs	48 Hrs
Group I. Operative controls		237 ± 10		180 ± 24*	191 ± 25*	205 ± 35‡
Group II. Infusion controls	Before Infusion		After Infusion			
A. Saline	236 ± 44		236 ± 44			
B. Dextran-40	261 ± 37		258 ± 30			
Group III. Experimental group				Before Infusion		After Infusion
A. Saline		250 ± 45		190 ± 39*		193 ± 50
B. Dextran-40		240 ± 34		190 ± 24*		231 ± 22†

*P <0.001
†P <0.005
‡P <0.025

Group III. Experimental group. Venous blood and expired respiratory gas samples were taken preoperatively and then 24 hours after operation both before and after infusion.

A. Saline Infusion (8 patients). 24 hours after operation these patients were given 1000 cc normal saline intravenously as a rapid infusion over 15 minutes.

B. Dextran-40 Infusion (10 patients). 24 hours after operation these patients were given 500 cc 10% dextran-40 in normal saline intravenously over 30 minutes.

Total body O_2 consumption was determined using a continuous O_2 consumption analyzer (Oxford Instrument Co., Oxford, Miss.). Ten minute expired respiratory air samples were collected in a weather balloon. Minute volume was determined by having the patient breathe through a volume spirometer. A sample of the expired air was analyzed and the difference between O_2 content in the expired air and that in room air determined. Total body O_2 consumption per minute was then calculated.

Whole blood (WB), plasma (P), and packed cell (PC) viscosities were measured on heparinized venous blood at 37.0 C using a Brookfield synchrolectric microviscometer (Model LVT) with special adapter for small samples. While WB viscosity was being determined, plasma and red cells in the remainder of the blood sample were being separated by centrifugation of whole blood at 1150 xG for 30 minutes. Viscosities were then determined on the plasma and the packed cell mass separately.

Hematocrits were performed using standard techniques. Plasma total protein concentrations were determined using the direct Biuret method.[15] Albumin and fibrinogen concentrations were determined by the specific salting out procedure and the Biuret reaction.[6,14]

Comparisons were made between pairs of observations by comparing the means of paired differences using Student's t-test.

Results

Group I. Total body O_2 consumption decreased uniformly in all patients after operation (Table 1). When compared to normal preoperative O_2 consumption the O_2 consumption 6 hours after operation had fallen to 76% of normal. Twenty four hours after operation O_2 consumption was 81% of normal (Fig. 1) and 48 hours after operation it was 87% of normal.

Changes in hematocrits and concentrations of plasma proteins were similar to those previously reported in another study (Table 2).[22]

Group II. Infusion of normal saline or dextran-40 into preoperative patients did not affect O_2 consumption (Table 1). However statistically significant decreases in hematocrits and measured plasma protein concentrations occurred (Table 3). WB viscosities dropped (Table 4), but P viscosities did not change; both were consistent with values previously published.[21] PC viscosities decreased after dextran-40 infusion and were statistically significant at a shear rate of 1.15 sec.$^{-1}$ Comparison of postinfusion WB viscosities with those noted before infusion (Fig. 2) revealed that the average per cent decrease in WB viscosities in those patients given saline was essentially the

TABLE 2. *Blood Viscosity Determinants in Group I Control Patients*

	Preoperative	Postoperative		
Hematocrit (%)	39 ± 3	35 ± 4*	35 ± 5*	33 ± 6§
Total plasma protein (gm%)	7.5 ± 0.3	6.8 ± 0.5§	7.0 ± 5†	6.9 ± 0.6§
Albumin (gm%)	3.5 ± 0.4	3.3 ± 0.4*	3.2 ± 0.3§	3.0 ± 0.4″
Fibrinogen (mg%)	496 ± 122	413 ± 122	468 ± 89	517 ± 33

*P <0.05 ″P<0.001
†P <0.025 § <0.005

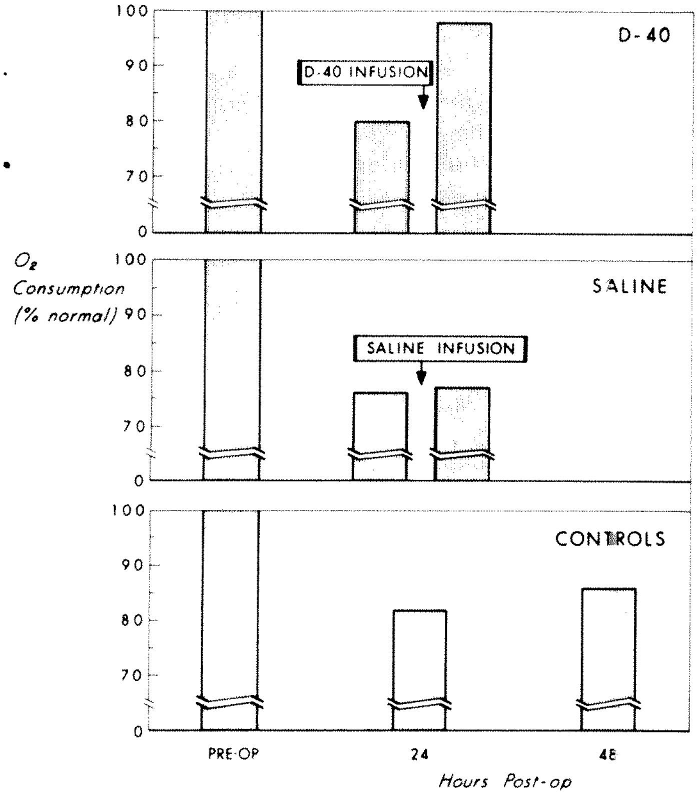

FIG. 1. O_2 consumption in postoperative patients. A uniform reduction in total body O_2 consumption was noted 24 hours and 48 hours after operation (bottom). Normal saline infusion had no effect on this diminished O_2 consumption (center), but when intravascular cellular aggregates were resolved by dextran-40 infusion, O_2 consumption returned to normal (top).

same at all shear rates studied while the decrease in patients given dextran-40 was more marked at the low shear rates.

Group III. O_2 consumption decreased after operation in all patients in this group (Table 1). Saline infusion had no effect on this decreased O_2 consumption, but dextran-40 uniformly returned O_2 consumption to normal.

When the normal average preoperative O_2 consumption in the saline group was compared to the O_2 consumption of this same group 24 hours after operation, it was found that O_2 consumption had fallen to 76% of normal (Fig. 1); after saline infusion it did not change and was 77% or normal. In the dextran-40 group average O_2 consumption 24 hours after operation was 80% of normal; after dextran-40 infusion it returned to 98% of normal.

Postoperative changes in hematocrits and measured plasma protein concentrations 24 hours after operation before infusion were not of statistical significance (Table 5); however infusion of either saline or dextran-40 led to statistically significant decreases in all of these parameters. Changes in those patients infused with dextran-40 were more marked than those in patients infused with saline.

WB viscosity also dropped after infusion of either saline or dextran-40 (Table 6). At all shear rates studied, when WB viscosities after infusion in the saline group were compared to the preinfusion WB viscosities, changes were proportional to the decrease in hematocrit (Fig. 3). The decreases seen in patients infused with dextran-40 were proportionately greater at the low shear rates and were out of proportion to those seen in the patients given saline. P viscosities were measured at 115 sec^{-1}; these decreased slightly after saline (1.5 ± 0.1 to 1.4 ± 0.1 cps) ($P<0.05$). and increased slightly after dextran-40 (1.5 ± 0.1 to 1.6 ± 0.1 cps) ($P<0.05$) PC viscosities increased uniformly 24 hours after operation (Table 6). Slight decreases after saline infusion were not statistically significant; however after dextran-40 infusion statistically significant decreases occurred at shear rates of 1.15 sec^{-1} and 2.30 $sec.^{-1}$.

Discussion

Surgical trauma in animals causes intravascular cellular aggregation and an increase in PC viscosity.[17] This in turn leads to capillary stasis and a decrease in total body O_2 consumption. When these intravascular aggregates are resolved by infusion of dextran-40, capillary circulation is restored and PC viscosity and O_2 consumption return to normal.[18]

It has been demonstrated in humans also that PC viscosity increases shortly after a severe surgical operation and that this increase persists for at least 48 hours.[22] In the present research, it has been further demonstrated that these changes are associated with a decrease in total body O_2 consumption which persists for at least 48 hours after operation.

TABLE 3. *Blood Viscosity Determinants in Group II Patients Infused Before Operation*

	Saline		Dextran-40	
	Before Infusion	After Infusion	Before Infusion	After Infusion
Hematocrit (%)	40 ± 2	35 ± 2 ‡	40 ± 2	33 ± 2 ‡
Total plasma protein (gm%)	8.7 ± 0.5	6.6 ± 0.6*	7.5 ± 0.3	5.8 ± 0.3‡
Albumin (gm%)	4.5 ± 0.3	3.8 ± 0.3‡	4.0 ± 0.3	2.8 ± 0.2‡
Fibrinogen (mg%)	500 ± 54	454 ± 41 *	496 ± 37	391 ± 79 †

*$P<0.02$, †$P<0.005$, ‡$P<0.001$

TABLE 4. *Blood Viscosities in Group II Patients Infused Before Operation*

Shear rate (sec^{-1})	Saline		Dextran-40	
	Before Infusion	After Infusion	Before Infusion	After Infusion
		Whole Blood Viscosity (cps)		
230.00	4.1 ±0.5	3.3 ±0.4#	4.4 ±0.5	3.6 ±0.2*
115.00	4.6 ±0.5	3.6 ±0.5#	4.9 ±0.6	4.1 ±0.5*
46.00	5.5 ±0.6	4.0 ±0.8#	5.8 ±0.8	4.6 ±0.3*
23.00	6.1 ±0.7	4.5 ±0.8#	6.8 ±1.0	5.2 ±0.5*
11.50	7.6 ±0.8	5.4 ±1.0#	8.6 ±1.7	6.1 ±0.7*
		Packed Cell Viscosity (cps)		
11.50	158 ±19.9	153 ±23.1	158 ±10.2	149 ±10.5
5.80	193 ±23.4	196 ±26.9	193 ±15.2	182 ±12.6
2.30	278 ±32.5	287 ±24.9	274 ±21.4	257 ±18.6
1.15	382 ±41.4	402 ±56.7	387 ±37.3	361 ±31.2†

$^*P < 0.001$ $^\dagger P < 0.05$

As previously noted in animal research,[18] saline infusion after operation had little or no effect on PC viscosity; however resolution of intravascular aggregates by dextran-40 infusion led to a decrease in PC viscosity to normal. As small vessel blood flow was restored, O_2 consumption returned to normal.

Resolution of intravascular cellular aggregates after dextran-40 infusion may result from induction of an increased plasma volume and hemodilution. For this reason saline was infused in this research in an amount equal to twice the volume of infused dextran-40. From the hematocrits shown in Tables 3 and 5, it is apparent that the dilutional effect of 1000 cc normal saline was less than that of 500 cc 10% dextran-40 in normal saline. However the effect of dextran-40 on PC viscosity at low shear rates was out of proportion to the dilutional effect noted after saline infusion.

When the average WB viscosity after saline infusion was compared to either the preoperative normal or the postoperative WB viscosity, the same proportionate decrease in WB viscosity was noted at all shear rates (Figs. 2 and 3). On the basis of the curve plotted from these data, it can reasonably be concluded that this effect was due to hemodilution. However, when such comparisons

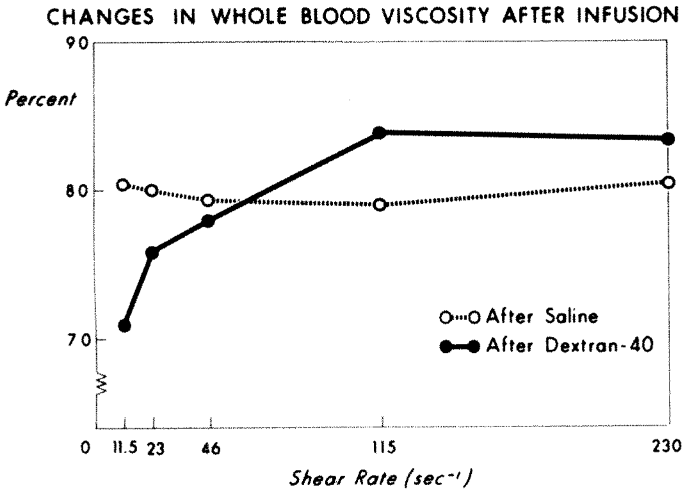

FIG. 2. When normal saline was infused into preoperative patients, whole blood viscosity decreased by the same per cent at all shear rates and in proportion to the degree of hemodilution. After dextran-40 infusion, however, whole blood viscosity decrease was disproportionately greater at the lower shear rates. Post-traumatic intravascular aggregation had not occurred in these patients so that O_2 consumption did not change.

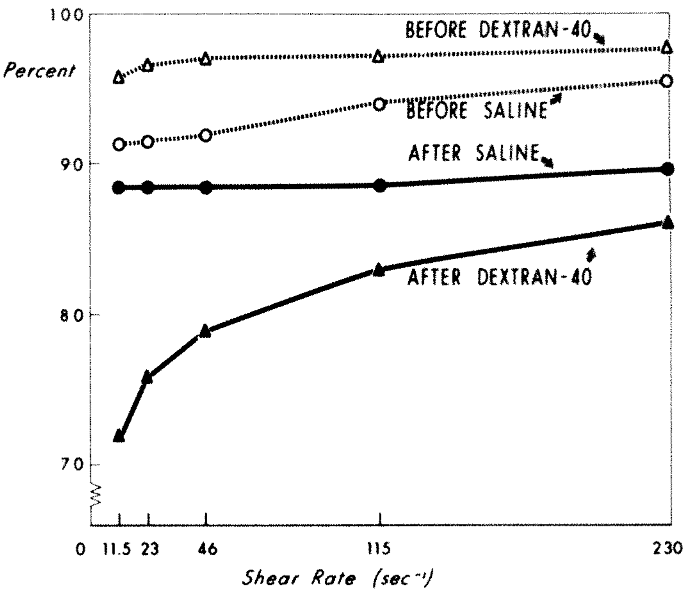

FIG. 3. When normal saline was infused to patients postoperatively, whole blood viscosity decreased by the same per cent at all shear rates and in proportion to the drop in hematocrit. After dextran-40 infusion, however, the decrease in whole blood viscosity at lower shear rates was much greater and was markedly out of proportion to the fall in hematocrit. This change occurred at the low shear rates, was localized to the packed cell moiety, and was accompanied by a return of O_2 consumption to normal.

TABLE 5. *Blood Viscosity Determinants in Group III Patients Infused After Operation.*

	Saline			Dextran-40		
	Preop	Postop		Preop	Postop	
		Before Infusion	After Infusion		Before Infusion	After Infusion
Hematocrit (%)	39 ± 2	37 ± 4	34 ± 3†	38 ± 3	38 ± 3	31 ± 2†
Total plasma protein (gm%)	7.4 ± 0.6	6.9 ± 0.6	6.3 ± 0.8‡	7.4 ± 0.6	6.6 ± 0.8	5.5 ± 1.2§
Albumin (gm%)	4.3 ± 0.3	3.8 ± 0.6	3.3 ± 0.5‡	3.9 ± 0.5	3.3 ± 0.3	2.3 ± 0.2§
Fibrinogen (mg%)	498 ±54	498 ±26	463 ±53†	499 ±52	483 ±48	400 ±56§

†P <0.02, ‡P <0.005, §P <0.001

were made for the patients infused with dextran-40, an asymtotic curve resulted. In the latter case, effects noted at the lower shear rates were markedly out of proportion to those seen in the saline infused patients in whom the viscosity effect was purely hemodilutional.

This disproportionate effect of dextran-40 on blood viscosity which was most marked at the lower shear rates, occurred not only in patients who had an increase in blood viscosity after operation (Fig. 3) but also in patients before operation, into whom dextran-40 was infused (Fig. 2). The effect was quantitatively similar in both groups and was confined to the packed cell moiety. In the former group the dextran-40 caused a return of PC viscosities to normal levels while in the latter PC viscosities decreased from normal to below normal levels.

Because the efficiency of small vessel circulation is essentially separate and different for plasma and for red cells, WB, P, and PC viscosities were considered separately in this investigation.[16,18,26] Hematocrit is the most important factor partially affecting human WB viscosity at the high shear rates studied;[4,20,21,27,31,32] such shear rates occur in large blood vessels. It was demonstrated in previous research and again confirmed in these experiments that WB viscosity drops postoperatively when hemodilution occurs.[22] However, many other factors are of equal importance in producing blood viscosity changes in small arterioles, capillaries and venules.[7-9,16,20,24] The low shear rates studied in the present research are those which most commonly occur in these smaller blood vessels.

Cellular aggregation leads to an increase in blood viscosity at low shear rates.[2,3,11-13,24,32] Such aggregates are confirmed to the packed cell moiety, and this probably accounts at least partially for the increased PC viscosities noted postoperatively in the present research. Furthermore, since intravascular cellular aggregates cause capillary stasis and decreased O_2 consumption and since capillary circulation is restored and O_2 consumption returns to normal when aggregates are resolved, it seems reasonable to assume that under certain circumstances intravascular cellular aggregates may be of considerable physiologic importance. That the ultimate clinical effect of diminished capillary blood flow caused by such aggregates might possibly be shock, cardiac arrest, metabolic

TABLE 6. *Blood Viscosities in Group III Patients Infused After Operation*

Shear rate (sec^{-1})	Saline			Dextran-40		
	Preop	Postop		Preop	Postop	
		Before Infusion	After Infusion		Before Infusion	After Infusion
			Whole Blood Viscosity (cps)			
230.00	4.0 ±0.3	3.8 ±0.4	3.4 ±0.3	4.0 ±0.5	4.0 ±0.4	3.4 ±0.3†
115.00	4.5 ±0.4	4.2 ±0.5	3.8 ±0.4	4.5 ±0.5	4.4 ±0.4	3.7 ±0.3†
46.00	5.3 ±0.6	4.9 ±0.7	4.3 ±0.6	5.2 ±0.7	5.0 ±0.5	4.0 ±0.5†
23.00	6.0 ±0.9	5.5 ±0.7	4.9 ±0.6*	6.0 ±0.7	5.8 ±0.7	4.5 ±0.6†
11.50	7.5 ±1.0	6.6 ±1.0	5.9 ±0.9	7.3 ±1.4	7.0 ±1.1	5.1 ±0.8†
			Packed Cell Viscosity (cps)			
11.50	149 ±14.0	160 ±13.6	154 ±10.0	151 ± 9.5	162 ±11.6*	156 ±12.0
5.80	183 ±17.0	198 ±17.4	187 ±14.3	186 ±11.4	201 ±18.2	192 ±17.4
2.30	262 ±28.2	297 ±28.9*	278 ±23.8	261 ±21.5	312 ±44.8§	267 ±26.3‡
1.15	361 ±41.5	452 ±61.9§	419 ±45.5	362 ±33.7	447 ±65.8¶	377 ±40.5‡

*P <0.05
†P <0.025
‡P <0.02
§P <0.01
¶P <0.005

acidosis or lack of proper wound healing appears to be a justifiable conclusion.[23,29]

In certain surgical patients other clinical effects of an increased blood viscosity are more clearcut. Dormandy and Hoare found in patients with vascular disease that WB viscosity was 13% higher in patients with intermittent claudication than in a similar group of controls.[10] They also found in these patients a higher incidence of coronary and peripheral arterial and venous thromboses, a more rapid progress of previously existent arteriosclerotic vascular disease, and a 20% greater failure rate in peripheral arterial operative procedures. In other patients who developed venous thrombosis after elective surgery, WB viscosity was significantly higher than in those who did not have such thrombosis.

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Surgical Technique for Creation of an Arteriovenous Fistula Using a Looped Bovine Graft

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We have used bovine grafts in a looped configuration in the forearm in 150 patients for chronic hemodialysis and have evolved a simple technique for their successful implantation. The critical technical points include: 1) use of large-diameter long grafts (7.0-8.0 mm diameter; 34-40 cm in length); maintenance of the heterograft in a distended and pulsating state throughout the procedure to prevent distortion and twisting; 3) creation of a wide smooth-looped tunnel with Bakes dilators; and 4) anastomosis to the largest available antecubital vein. Thirteen cases of late graft occlusion (3-36) months) have been found to be produced by a localized obstructive lesion just distal to the venous anastomosis. These grafts were easily restored to a functional status by thrombectomy and patch graft angioplasty of the stenotic segment. The looped graft technique is not applicable to all patients requiring hemodialysis but it is especially helpful when distal vessels have been obliterated by previous procedures or when home-dialysis is planned. This surgical technique should be among the alternatives considered by surgeons concerned with problems of vascular access in patients with chronic renal failure.

MAINTENANCE of a safe mode of vascular access is a crucial consideration for the lives of thousands of patients currently sustained by hemodialysis. The necessary repeated use of extremity vessels in circuits involving direct needle punctures, prosthetic shunts, or arteriovenous fistulae frequently culminates in a difficult situation in which chronic hemodialysis is still needed, but a method of surgical construction of a mode of access is not obvious. The implantation of modified bovine carotid arteries recently has developed as one of the helpful adjunctive techniques for creating an arteriovenous fistula in these critical situations.[1,3,6,11,13]

Whether or not the graft is inserted in a straight or looped configuration is dependent upon: 1) the status of the patient's distal vessels; 2) hemodynamic considerations; and 3) the surgeon's experience and preference. The looped technique is more complicated than the straight-graft method, but in selected situations, it is superior and even necessary. The surgical procedure for implanting a looped vascular graft has not previously been described in detail. It is quite likely that this lack of standardization is an important reason why there have been quite contradictory results reported with the loops.

We have used modified bovine grafts to form a looped arteriovenous fistula in 150 patients requiring chronic hemodialysis. It is the purpose of this report to outline a reliable and simple technique that has evolved from this experience.

Method

The entire upper extremity is prepared and draped. Local anesthesia is obtained with 0.5% lidocaine 1 cm below the antecubital crease. A transverse incision is made over the brachial artery pulse and this vessel is exposed for a distance of 3 cm (Fig. 1a). The median cubital vein, or a large vena comitante of the brachial artery, is selected and isolated (Fig. 1b). The bovine graft is removed from its container and rinsed thoroughly with saline. We usually use grafts with a 7-8 mm diameter and

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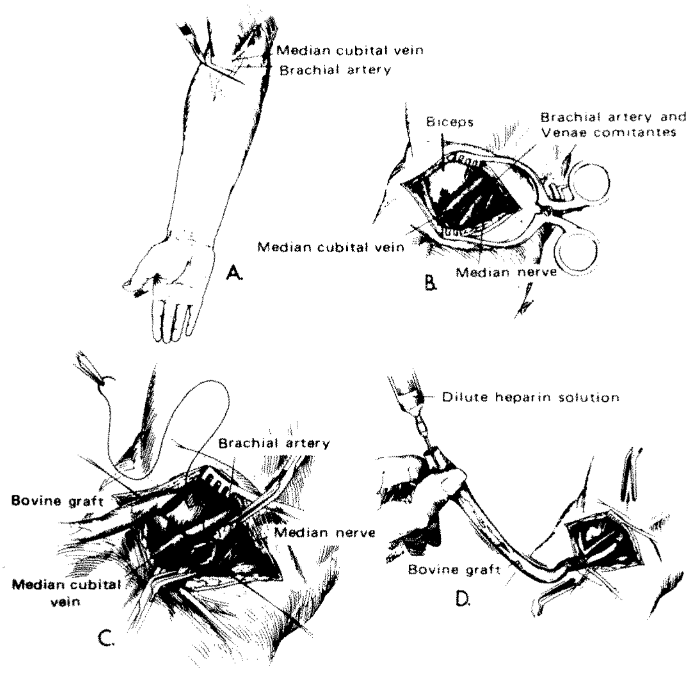
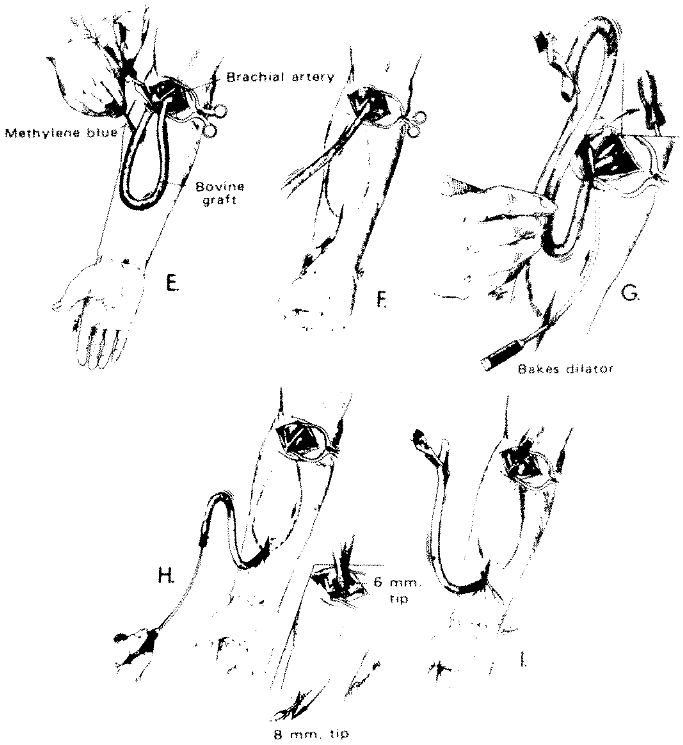


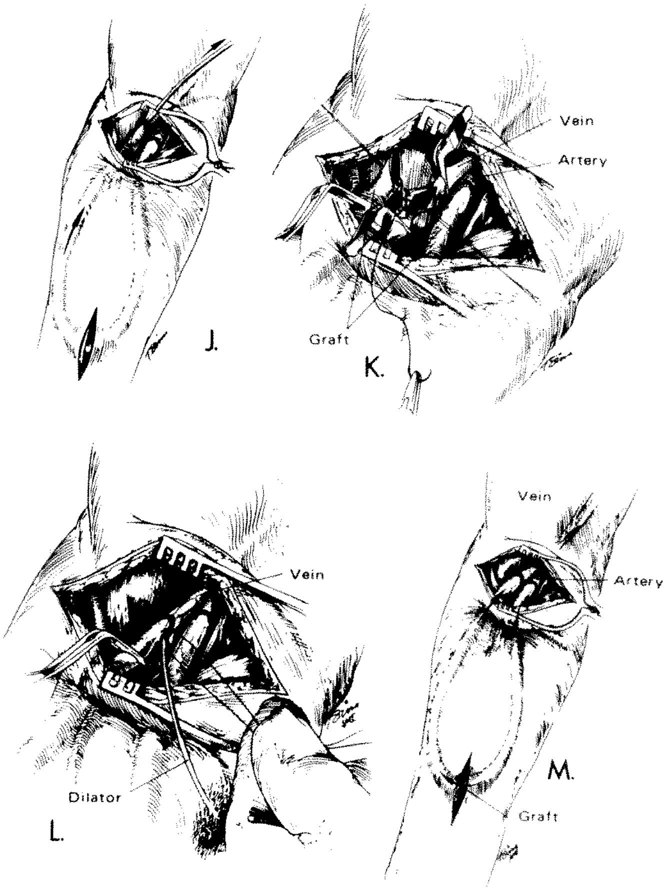
FIGS. 1 A-D. Method of insertion of modified bovine carotid artery graft.



FIGS. 1 E-I. Tunneling procedure.

a length of 34-40 cm. The end of the bovine graft is beveled slightly and sutured end-to-side to the brachial artery using 5-0 or 6-0 polypropylene (Fig. 1c). The graft is filled with dilute heparin solution and the end of the graft is occluded (Fig. 1d). The bovine graft is kept distended and allowed to pulsate during the remainder of the operation to prevent any twisting or distortion during the tunneling procedure. The graft is placed on the forearm to outline a smooth curve to the vein in the antecubital fossa. This route is traced on the skin with methylene blue and the underlying subcutaneous tissue is infiltrated with lidocaine (Fig. 1e). The distal skin incision is then made (Fig. 1f). A subcutaneous tunnel is created with an 8 mm Bakes dilator which is shaped by the surgeon to conform to the smooth curve outlined on the skin. The graft is then secured to the dilator and pulled through the tunnel (Fig. 1g&h). The tunneling and pull-through procedure can further be simplified by using a Noon dilator that has opposing 8 mm and 6 mm ends (Fig. 1h). These identical maneuvers are then performed for the ascending limb of the loop (Fig. 1i&j). The graft is not clamped proximally so that it will remain distended to prevent any twisting. The anastomosis between the bovine graft and the vein is performed using 5-0 or 6-0 polypropylene suture (Fig. 1k). Just prior to completing the anastomosis, the vein is gently dilated proximally and distally and then the suture is tied (Fig. 1l). At the completion of the procedure, the graft lies in a subcutaneous plane and forms a smooth loop. (Fig. 1m).

Looped arterial heterografts on the volar aspect of the



FIGS. 1 J-M. Pull-through procedure.

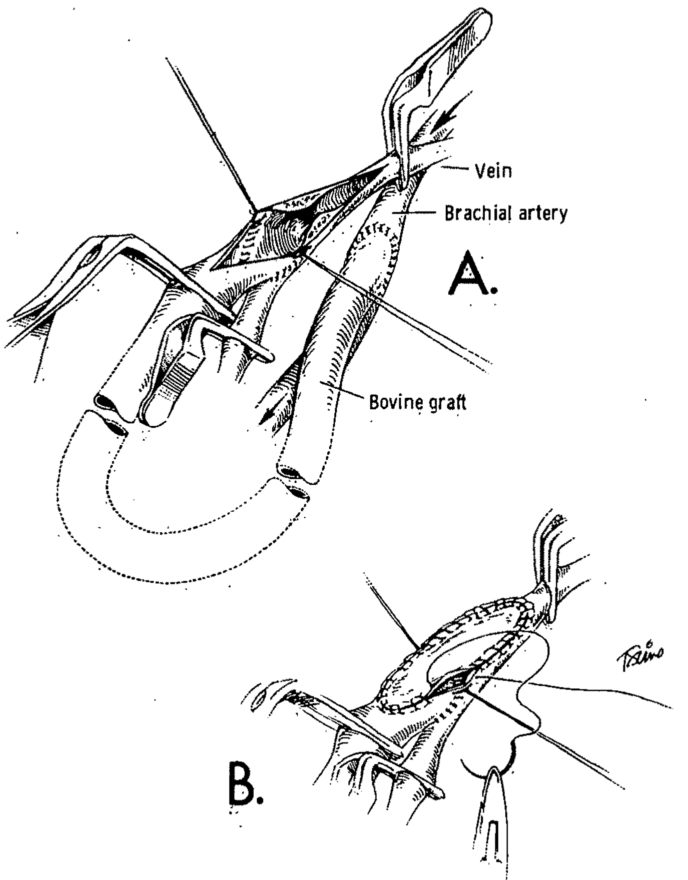


FIG. 2. Localized stenosis at the outflow tract of the looped bovine graft (A). Horizontal mattress sutures are placed laterally and medially across the previous anastomosis. A small piece of autogenous vein is utilized to widen the obstructed area by performing a patch-graft angioplasty (B).

arm are especially easy to cannulate for hemodialysis because of the sparsity of subcutaneous tissue in this area. We suggest use of the graft be delayed for at least 14 days after implantation to allow time for tissue adherence and thus prevent a dissecting hematoma at the time of needle puncture.

Discussion

Looped forearm grafts have been used for vascular access in patients with chronic renal failure and inadequate wrist vessels since the original report by May et al. in 1969.[10] Substitution of modified bovine carotid arteries for autogenous saphenous veins, as first described, has a number of attractive features: 1) the operation is shortened and facilitated by using the readily accessible and reliable vascular heterografts; 2) the patient's saphenous vein is preserved for future cardiovascular operations; 3) the occasionally uncomfortable removal of the saphenous vein under local anesthesia is eliminated and the added risk of general anesthesia is unnecessary; 4) the patency rate appears to be increased when the larger diameter (7-8.0 mm) bovine grafts are used instead of smaller venous autografts;[3,4,11] and 5) home dialysis is simplified by having a large pulsatile subcutaneous graft that is easy to cannulate with a needle.[1]

Other surgeons have reported superior results with straight rather than looped grafts and have judged the latter as a poor choice and even empirically condemned the technique as "hemodynamically wrong."[6] The recent experimental work of Lavigne et al., on the contrary, has suggested that the hemodynamic characteristics of looped grafts are excellent and they have concluded that this type of fistula is indeed preferred in certain situations because the loop preserves normal distal limb perfusion and does not induce retrograde arterial flow when there is no significant proximal arterial stenosis.[9]

We have found that the forearm loop also has the important long-term advantage of allowing use of a longer segment of graft than can be employed with the straight implant. When inserting the loop, as described in this report, we usually have been able to use the entire 34-40 cm graft. The straight graft between the wrist and the antecubital area or between the infra-axillary vessels and the antecubital zone generally results in a graft that is 8-20 cm shorter than the looped graft. This difference is graft length results in a considerably smaller area for repeated needle punctures in these patients who require dialysis 2 to 3 times per week for several years.

One special problem that deserves particular attention is the surgical management of late graft thrombosis. Thirteen of the 150 patients in whom we have used looped forearm heterografts have developed delayed (3-36 months) thrombosis due to localized stenosis just distal to the anastomosis between the bovine graft and the patient's forearm vein. This process is similar to that described by Merickel et al. as "pseudodiaphragm formation"[11] and by others who have found identical lesions on the outflow side of a variety of high pressure-flow systems, e.g. silastic arteriovenous shunts,[12] aortorenal artery grafts, and bypass grafts from the aorta to the femoral arteries.[7] This stenotic area has been shown to be produced by: 1) reactive hyperplasia and fibrosis of the intima and muscularis of the vein due to the effects of arterial pressure on the thin wall;[2] 2) local injury to the venous intima followed by fibrin deposition and thrombosis;[5] or 3) formation of an obstructive plaque resembling an atherosclerotic lesion in the vein itself.[8] The graft can readily be restored to a functional status by immediate thrombectomy with a Fogarty catheter and venous patch graft angioplasty of the segmentally obstructed area (Fig. 2).

Looped forearm heterografts have provided an easy and reliable system for hemodialysis. The operation, of course, will not be applicable to all patients requiring prolonged vascular access, but it should be among the techniques considered by surgeons involved in the management of patients with chronic renal failure in whom a simple and safe system of repeated vascular access is the foundation needed for a comfortable life.

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John M. Wehner, Jr., *Business Manager*

Letters to the Editor

February, 1975

Dear Editor:

Dr. Crile's article entitled, "Results of Conservative Treatment of Breast Cancer at Ten and Fifteen Years," in the January issue of The Annals is filled with evidences of gross bias in the form of favorable case selection for patients having his simple procedures. Some of his statistical methods are highly questionable and his conclusions are totally unwarranted by the presented facts.

These defects are in some instances obvious, but in others subtle and could easily be overlooked by uncritical readers. Since Crile's influence in this area is considerable, we feel that it is imperative that the illusory character of his case for limited surgical procedures for operable cancer of the breast be recognized.

The major faults in this presentation are as follows:

1. Crile's comparison of his results with those reported by the National Cancer Registry can hardly be considered an equitable one. Crile's patients were all treated in a private clinic by surgeons of extensive experience. The cases cited from the National Cancer Registry are reported from widely dispersed areas in three states from public as well as private hospitals and from a hundred or more small community hospitals. Many of the patients were operated on by surgeons of limited experience and not all had radical mastectomies as his Table 2 suggests or nearly all as stated in the text. The degree to which total survival figures are influenced by the inclusion of material from public hospitals is exemplified by figures from the Report from the California Tumor Registry[1] showing a 46% 10-year survival rate for all cases from private hospitals versus 21% in county hospitals, and for localized cases, 69% versus 41%. This same source shows that 16% of the surgically treated cases were not treated by radical mastectomy.

2. Crile's comparison of the cases of his patients treated by simple operations versus his version of a radical operation in terms of True Stage I or True Stage II categories is grossly misleading, especially for so-called True Stage I cases. True Stage I is defined as "those cases in clinical State I treated by a radical operation, in which, on microscopic examination no cancer is found in the axillary nodes; and those cases treated by partial or simple mastectomy in which on subsequent followup evidence of axillary nodal disease fails to appear." It would appear at first glance that comparison of end results of patients treated by two different methods and classified as True State I would be eminently fair, but this is emphatically not the case.

It is well established, as shown by Pickren[2] and Saphir and Amromin[3] that when axillary nodes removed in Clinical Stage I cases that are found to be free of cancer on routine examination are re-examined by more searching methods, 22% and 33% respectively were shown to contain metastatic cancer. In round numbers, one quarter of Crile's patients having a radical operation and classified as True Stage I are in fact, Stage II. On the contrary, patients having simple operations are proven by the passage of time to be True Stage I. The consequence of this is that the final comparison is made between *all* of the patients treated initially by the radical operation and only those having the simple operation who fail to develop axillary nodal disease in the interval. The failures in this respect are deleted since they no longer conform to the definition.

3. In Crile's matched pair study it is significant that only 6 of 42 patients (12%) in the partial mastectomy group had axillary dissection at the time of the initial operation in contrast with 26 of 42 or 51% of patients having total mastectomy. Crile has repeatedly emphasized the point that axillary dissection is carried out

only when axillary nodes are considered to be clinically positive. Crile's statement that 19 of 42 patients in the partial mastectomy group had involved nodes requires some explanation since only 9 altogether and 6 initially had axillary dissection and some of these must have had negative nodes. Furthermore, it should be recognized that a 40% 10-year survival for a highly selected series consisting of small peripheral tumors having an average diameter of only 2.1 cm is a conspicuously poor survival figure for clinical material of this kind.

4. But the most glaring evidence of Crile's extensive bias in the form of favorable case selection for his simplified procedures is revealed in the statement: "The small difference in 5 and 10-year survival rates, 11% in favor of the simple operations at 5 years and 4% at 10 years, can be explained by selection, for the average diameter of the cancers treated by modified radical mastectomy was 3.1 cm compared to 2.1 cm for those treated by simple mastectomy." This is a *huge* difference in size. A cancer 3.1 cm in diameter is by volume more than three times larger than one 2.1 cm in diameter.

Crile's conclusion that the figures he has presented suggest that conservative and radical operations give the same survival rate at 10 and 15 years is totally unwarranted. The correct and logical conclusion is that, despite the massive disadvantage resulting from the fact that the cancers comprising the radically treated series were more than three times larger than those having simple operations, the survival rate at 15 years was, nevertheless, equally good. This was so despite the fact that the radical operations were not standard radical mastectomies, but were substandard modified radical mastectomies in which skin flaps were cut thick and the axillary dissection was, as Crile describes it, "purposely incomplete."

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March 10, 1975

Dear Editor:

Doctor Anglem has long been my most effective and respected critic. I begin by saluting his continuing efforts, and I continue by rebutting them.

1. Anglem says that to compare the National Cancer Registry's results with those of the Cleveland Clinic is inequitable, because many of the National Registry's patients were operated on by inexperienced surgeons.

I reject this conclusion because Haagensen has reported that the survival rate obtained by his residents was a little higher than his own, and Smith and Meyer[1] found the survival rate 1% higher after operations by "occasional operators" as compared to "experienced surgeons." In the treatment of cancer of the breast it is the morbidity, not the survival rate, that is affected by the skill of the surgeon.

Anglem also points out that not all of the Registry's patients were treated by radical mastectomy. Of course not. Not even Doctor Anglem would do a radical mastectomy on an 85-year-old woman in cardiac decompensation. If one considers only the patients treated by radical operations one automatically selects a group with a relatively favorable prognosis from the standpoint of death from causes other than cancer.

2. Anglem's second point is that it is unfair to call Pathologic Stage I cancer, proved by histologic examination of nodes, True Stage I. He may be right, but no one knows what happens to the micro-deposits of cancer that are demonstrated by serial section of nodes that on simple section have been declared to be free of cancer. studies have shown that survival rates are not affected by their presence. Does the cancer in these micro-deposits grow, or is it rejected? All I know is what we learned when we were basing our decision as to whether or not to dissect the axilla on preoperative clinical staging. In these cases the proportion of Clinical Stage I patients treated by axillary dissection and found to have nodes involved was the same as that of similarly staged patients whose axillae were not dissected and who later had appearance of cancer in nodes.

3. Anglem's third point indicates only that he has had no experience with partial mastectomy. One does not explore or dissect an apparently uninvolved axilla unless the primary tumor is in the outer quadrant. For this reason there are fewer immediate axillary dissections in the partial mastectomy group. Furthermore, in the period in which these patients were being treated, half of the total mastectomies were being done by surgeons who always did an axillary dissection regardless of whether or not there was palpable involvement of nodes.

4. Anglem's fourth point, the low 10-year survival rate in the patients treated by partial mastectomy, is valid, but in my article it is clearly explained that during this period of tentatively trying out partial mastectomy patients were being selected adversely. Many of them were selected because of age or infirmity. Both the text and the table in my article show that fewer patients in the partial mastectomy group died of cancer than in the controls.

5. Anglem's fifth point is one that I had already made by stating that "the staging of the two groups was not comparable."

The reason that I reported the 15-year survival rate of these patients was to show that the survival rate of patients with small tumors treated by partial mastectomy was better up to 10 years, but that it was discouraging to observe a relatively high incidence of distant metastasis between 10 and 15 years in patients with small Stage I cancers who never had invovlement of nodes or local recurrence of cancer.

6. Anglem's final point about incomplete axillary dissection and thick skin flaps has no bearing on the question of survival because our incidence of local recurrence was lower than that reported after radical mastectomy, only 6%. But it is distant metastasis, not local recurrence, that causes death. We believe that provided the incidence of local recurrence is low the reported differences in survival rates depend on the stage of the cancers in the patients selected for treatment rather than on the type of operation employed.

There was one misstatement in my article that escaped Doctor Anglem's penetrating inquiry. Just before "Discussion" I stated that "Two more had had immediate axillary dissection for involved nodes." If they had had immediate dissections the operations could not have been classified as simple. In reality one was treated immediately by radiation and the other by a 7 months' delayed axillary dissection. Neither had recurrence of tumor locally or in nodes.

I am grateful to Doctor Anglem and the Editors of Annals of Surgery for this opportunity to correct my misstatement.

George Crile, Jr., M.D.
Cleveland Clinic
Cleveland, Ohio 27710

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Book Reviews

The David Hume Memorial Symposium on Transplantation. Lawrence, Lee, Lower, Pierce, Wolf and Rapaport, Editors. New York, Grune and Stratton, 163 pages, 1975, $11.50.

THE PURPOSE AND DIRECTION of the *David M. Hume Memorial Symposium on Transplantation* was clearly set during the introductory remarks by Dr. Walter Lawrence when he related that the symposium was not to be a sentimental eulogy to the man, but would be reports from scientific inquiry for the benefit of man.

Billingham's chapter on "Reminiscences of a Transplanter" should be of interest to students of transplantation biology, as well as individuals of separate disciplines. The chapter relates Dr. Billinghams's three decades in this field which progressed from anecdotal experiences through in depth development of this exciting field. The original work of Medawar and his contributions in the 1940's to the present are presented with all the personal flavor that Dr. Billingham is so capable of interjecting.

Dr. Bernard Amos' discussion of the genetics of the human histocompatibility system is a classic chapter. Again, the reader is benefitted by the author's personal knowledge, growth and direction in this most complicated area. Amos clearly relates the historical development of the recognition of the HL-A antigens and parallels them with their analogs, H2 in mouse, and Ag-B in rat. Amos is able to take mixed leukocyte culture data and allograft rejection experiments and construct a series of genes that control different factors into a histocompatibility chromosomal region in man. Teraski is then able to relate histocompatibility and it's impact on clinical renal transplantation with a computer analysis of several thousand patients. Rapaport then discusses cross-reacting antigens with the HL-A system and possible links with the immunosuppressed patients and the development of a spontaneous malignancy. Basic experimental evidence in immunosuppressed animals that develop malignancy is alluded to by Schwartz in a brief but informative chapter that would support Rapaport's discussion in man.

Williams' chapter on the clinical aspects of allograft rejection is beautifully done. Again, the reader can clearly sense that the topics are discussed by authors with an in-depth personal experience which makes the chapters even more convincing.

Kountz and Belzer author quite practical chapters which deal with the mechanics, at the present time, of establishing a clinical transplantation service for a major medical center.

Lower and Starzl review the current status and future of cardiac transplantation and orthotopic liver transplantation. These chapters reflect the responsible and critical analysis offered by present day pioneers in this most complicated area. Thomas' chapter is extremely important, in that it not only reports the only meaningful clinical experience with bone marrow transplantation, but it quite clearly focuses on the lack of complete understanding of the major histocompatibility complex in man. Thomas demonstrates that HL-A identity and MLC identity between donor-recipient pairs when one is dealing with immunocompetent cells is not heralded by uniform success. The relatively high instance of graft versus host disease between these sibling pairs, clearly documents that a complete understanding of this chromosomal region in man has not been recognized and defined.

Russell's discussion of the future of constructive surgery not only places present clinical transplantation in the proper prospective, but goes on to give a very elegant and scholarly discussion about the possible future of clinical transplantation.

Moore, Merrill and Murray end the symposium monograph with a very personal and interesting chapter concerning the life and contributions of David Hume that all readers should find both stimulating and interesting.

HILLIARD F. SEIGLER, M.D.

Myelography (3rd edition). Robert Shapiro, 602 pages, Chicago, Year Book Medical Publishers, 1975, $42.50.

IN THIS THIRD EDITION, Shapiro continues this book's tradition as the most comprehensive thesis on the subject of myelography. The text now not only includes excellent discussions of the history, methodology, and interpretation of positive contrast myelography but also includes new sections on arteriography and pneumography of the spine. A generous number of well-selected illustrations of excellent technical quality are included. Sketches accompany many of the radiographs to assist the reader with interpretation of the anatomy of myelographic patterns. The text appropriately stresses the usefulness of placing the patient in the supine position for myelography when dorsal cord lesions are suspected. The brief chapter on diskography complements the limited role this exam plays in the diagnosis of spinal disorders.

Only a few areas are incompletely discussed. A useful practice not mentioned by the author is the placing of a scratch on the skin (off from the midline) at the level of a myelographic block, to aid the surgeon later in the situation of an incision at the time of surgery. Perhaps more stress should have been placed on the particular usefulness of air myelography in the localization of upper cervical canal lesions.

This book remains an excellent text and reference source for neurology, neurosurgery, orthopedic, and radiology residents and contains discussions of numerous conditions in which myelography plays an important diagnostic role.

M. STEPHEN MAHALEY, JR., M.D.

Recent Advances in Pediatric Surgery. Andrew W. Wilkinson, editor, 220 pages, New York, Longman, Inc., 1975, $24.50.

DR. WILKINSON has selected sixteen subjects in the field of pediatric surgery where recent developments have a significant influence on surgical care and treatment. One chapter is devoted to each subject. Each chapter is by an individual author and each author is an authority in his respective field. The material is well illustrated and is presented in a clear, concise form to make for interesting reading.

The subjects which Dr. Wilkinson has selected are timely and significant. Included are sections on genetics, sickle cell disease, hemophilia, intensive care, pulmonary function, cardiac surgery, myelomeningocele, renal failure, ureterovesical operations, biliary atresia, meconium ileus, mechanical sutures, laryngeal stenosis, chemotherapy for solid tumors and clinical immunology.

The book can be highly recommended for any surgeon whose practice includes any of the categories so authoritatively reviewed in this concise volume.

LESTER W. MATIN, M.D.

Physiology of the Kidney and of Water Balance. Deetjen, Boylan and Kramer, 141 pages, New York, Springer-Verlag, 1975, $8.80.

THIS TEXT, which is reportedly written for medical, dental and graduate students in physiology, is a very comprehensive and concise outline of the major components of the physiology of kidney and water balance. It covers a wide range of topics including: a) morphology of the kidney; b) function and structure of the nephron; c) kinetics of absorption and excretion of the tubular cells; d) details of renal hemodynamics; e) salt and water balance. The text is liberally documented with charts and graphs that aid the readers' understanding of the material presented. There is, however, a heavy component of mathematics and biochemical kinetics throughout the text which in some sections makes reading difficult at the medical student level. The readability of the text is also slightly impaired by the authors' intent to present an enormous amount of material in a concise form. There is relatively little material in the book as to the alterations of renal function during disease states. Individuals with a prior background in renal physiology will be most apt to find this text a useful review and reference source.

JAMES CERILLI, M.D.

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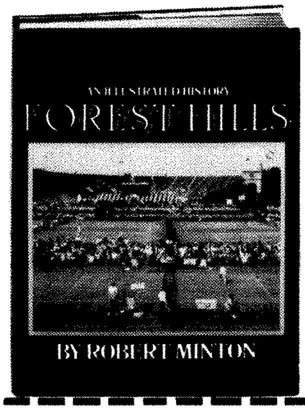

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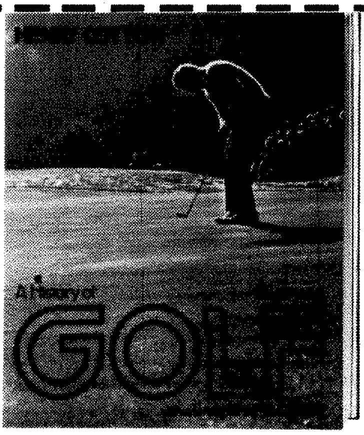

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Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

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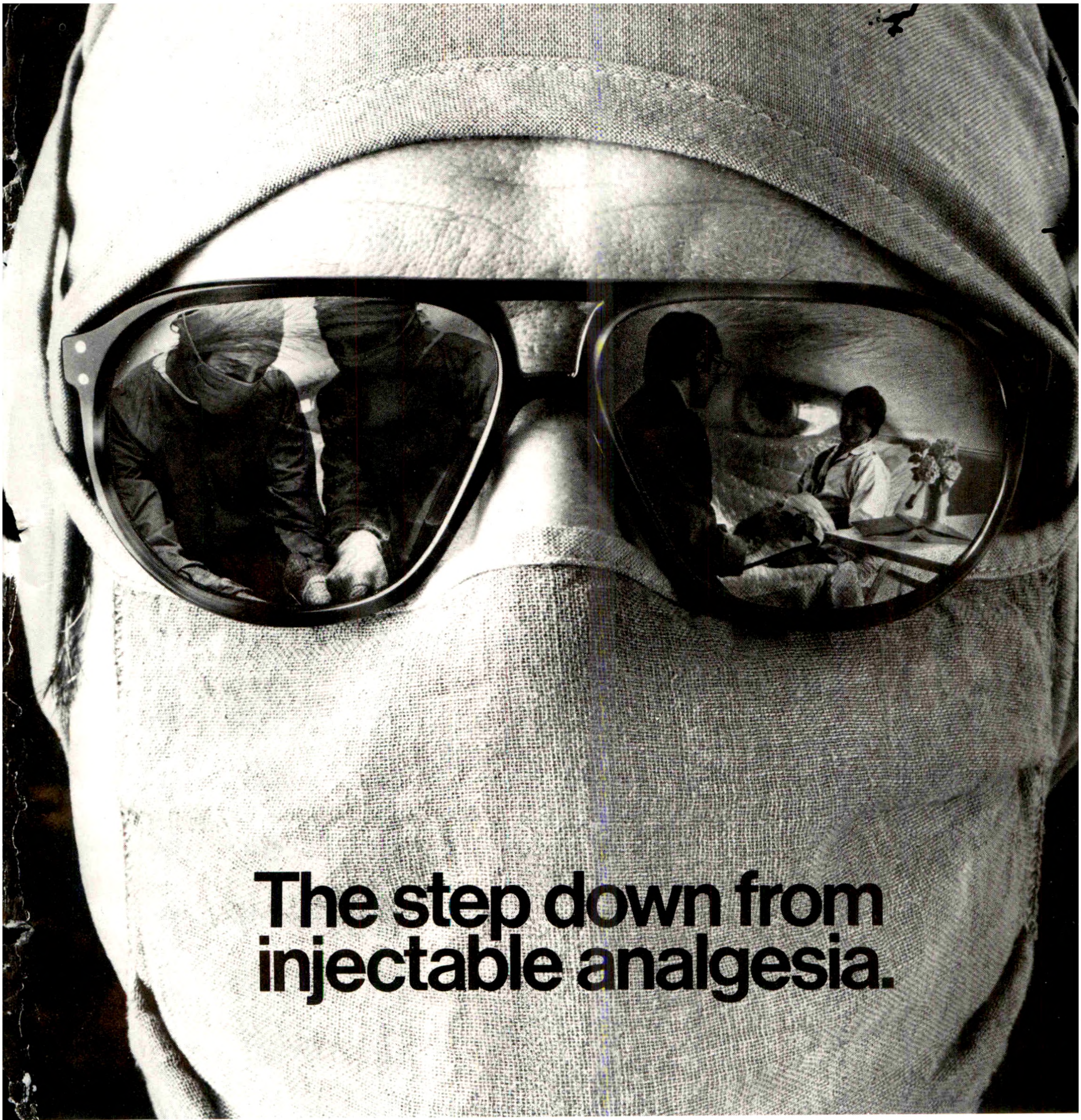
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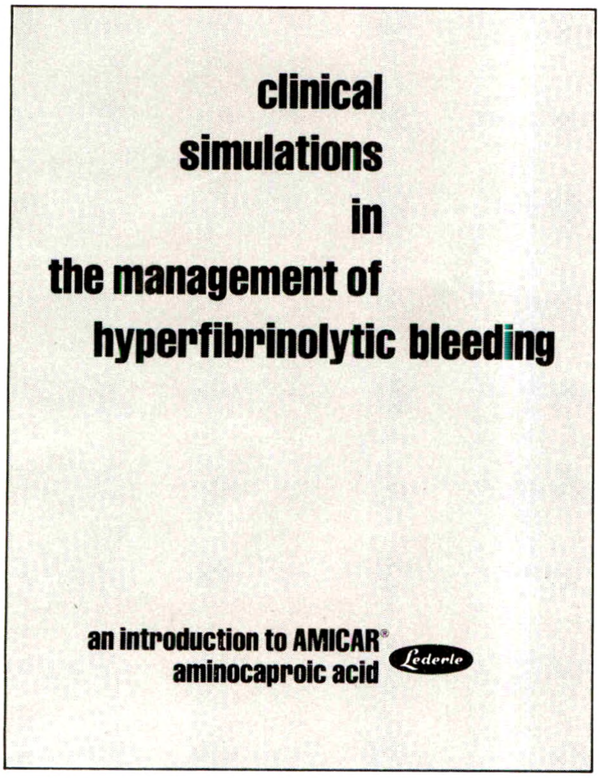

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This review of hyperfibrinolytic bleeding is both conceptual and practical. The complete unit encompasses the concepts involved in hyperfibrinolytic bleeding, an experience in clinical problem solving, and a recommended course of therapy.

This program in continuing medical education meets the criteria for 2 hours of credit in category 5a for the Physicians Recognition Award of the American Medical Association.

STUDY METHODOLOGY

Analysis. Mr. O. has four-plus enlargement of the prostate. His specific medical history is given, as well as the general background of his condition. You will be asked to choose the appropriate tests—and based on the results—proceed to step two.

Surgical Decision. Which shall it be? Transurethral resection? Suprapubic prostatectomy? Perineal? Retropubic? Choose by marking the decision box. The latent image color reactor will tell you if you were right or wrong.

POSTOPERATIVE BLEEDING AND TREATMENT

Prostate bed is irrigated. All is well until the second postop day. Patient has begun to hemorrhage. Now the simulation presents you with almost a dozen different approaches for control of it. You must choose. The tests. The chemotherapy.

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AMICAR®

AMINOCAPROIC ACID

INTRAVENOUS • TABLETS • SYRUP

INDICATIONS: AMICAR has proved useful, in many instances, in the treatment of excessive bleeding which results from *systemic hyperfibrinolysis* and *urinary fibrinolysis*. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.

Systemic hyperfibrinolysis, a pathological condition, may frequently be associated with *surgical complications* following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; *hematological disorders* such as aplastic anemia, *abruptio placentae, hepatic cirrhosis, neoplastic disease* such as carcinoma of the prostate, lung, stomach, and cervix.

Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is *surgical hematuria* (following prostatectomy and nephrectomy) or *non-surgical hematuria* (accompanying polycystic or neoplastic diseases of the genitourinary system).

CONTRAINDICATIONS: AMICAR should not be used when there is evidence of an active intravascular clotting process.

WARNINGS: Safe use of AMICAR has not been established with respect to adverse effects upon fetal development. Therefore, it should not be used in women of child-bearing potential and particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the possible hazards.

PRECAUTIONS: AMICAR *aminocaproic acid* has a very specific action in that it inhibits both plasminogen activator substances and, to a lesser degree, plasmin activity. The drug should NOT be administered without a definite diagnosis, and/or laboratory findings indicative of hyperfibrinolysis (hyperplasminemia).*

*Stefanini, M. and Dameshek, W.: The Hemorrhagic Disorders, Ed. 2, New York, Grune and Stratton, pp. 510-514, 1962.

The use of AMICAR should be accompanied by tests designed to determine the amount of fibrinolysis present. There are presently available (a) general tests, such as those for the determination of the lysis of a clot of blood or plasma and (b) more specific tests for the study of various phases of fibrinolytic mechanisms. These latter tests include both semiquantitative and quantitative technics for the determination of profibrinolysin, fibrinolysin, and antifibrinolysin.

Animal experiments indicate particular caution should be taken in administering AMICAR to patients with cardiac, hepatic or renal diseases.

Demonstrable animal pathology in some cases have shown endocardial hemorrhages and myocardial fat degeneration. The use of this drug should thus be restricted to patients in whom the benefit hoped for would outweigh the hazard. Physicians are cautioned in the use of this product because of animal data showing rat teratogenicity and kidney concretions.

Rapid intravenous administration of the drug should be avoided since this may induce hypotension, bradycardia and/or arrhythmia.

One case of *cardiac* and *hepatic lesions* observed in man has been reported. The patient received 2 grams of aminocaproic acid every 6 hours for a total dose of 26 grams. Death was due to continued cerebral vascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

If it is accepted that fibrinolysis is a normal process, potentially active at all times to ensure the fluidity of blood, then it must also be accepted that inhibition of fibrinolysis by aminocaproic acid *may* result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of *intravascular clotting* which followed this treatment. Rather, it appears that such intravascular clotting was most likely a result of the fibrinolytic disease being treated.

It has been postulated that *extravascular clots* formed *in vivo* with incorporated aminocaproic acid may not undergo spontaneous lysis as do normal clots. However, it is the consensus of experts that the few reported cases of extravascular clotting could have occurred in the absence of aminocaproic acid treatment.

ADVERSE REACTIONS: Occasionally nausea, cramps, diarrhea, dizziness, tinnitus, malaise, conjunctival suffusion, nasal stuffiness, headache, and skin rash have been reported as results of the administration of aminocaproic acid. Only rarely has it been necessary to discontinue or reduce medication because of one or more of these effects.

Thrombophlebitis, a possibility with all intravenous therapy, should be guarded against by strict attention to the proper insertion of the needle and the fixing of its position.

DOSAGE AND ADMINISTRATION: *INITIAL THERAPY*—An initial priming dose of 5 grams of AMICAR administered either orally or intravenously followed by 1 to 1¼ gram doses at hourly intervals thereafter should achieve and sustain plasma levels of 0.130 mg./ml. of the drug. This is the concentration apparently necessary for the inhibition of systemic hyperfibrinolysis. Administration of more than 30 grams in any 24-hour period is not recommended.

INTRAVENOUS: AMICAR *aminocaproic acid* Intravenous is administered by infusion, utilizing the usual compatible intravenous vehicles (e.g. Sterile Water for Injection, physiologic saline, 5% dextrose or Ringer's Solution). RAPID INJECTION OF AMICAR INTRAVENOUS UNDILUTED INTO A VEIN IS NOT RECOMMENDED.

For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 16 to 20 cc. (4 to 5 grams) of AMICAR Intravenous be administered by infusion during the first hour of treatment, followed by a continuing infusion at the rate of 4 cc. (1.0 gram) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

ORAL THERAPY: If the patient is able to take medication by mouth, an identical dosage regimen may be followed by administering AMICAR Tablets or 25% Syrup as follows: For the treatment of *acute* bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 10 tablets (5 grams) or 4 teaspoonfuls of syrup (5 grams) of AMICAR be administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 gram) or 1 teaspoonful of syrup (1¼ grams) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.

REV. 7/72

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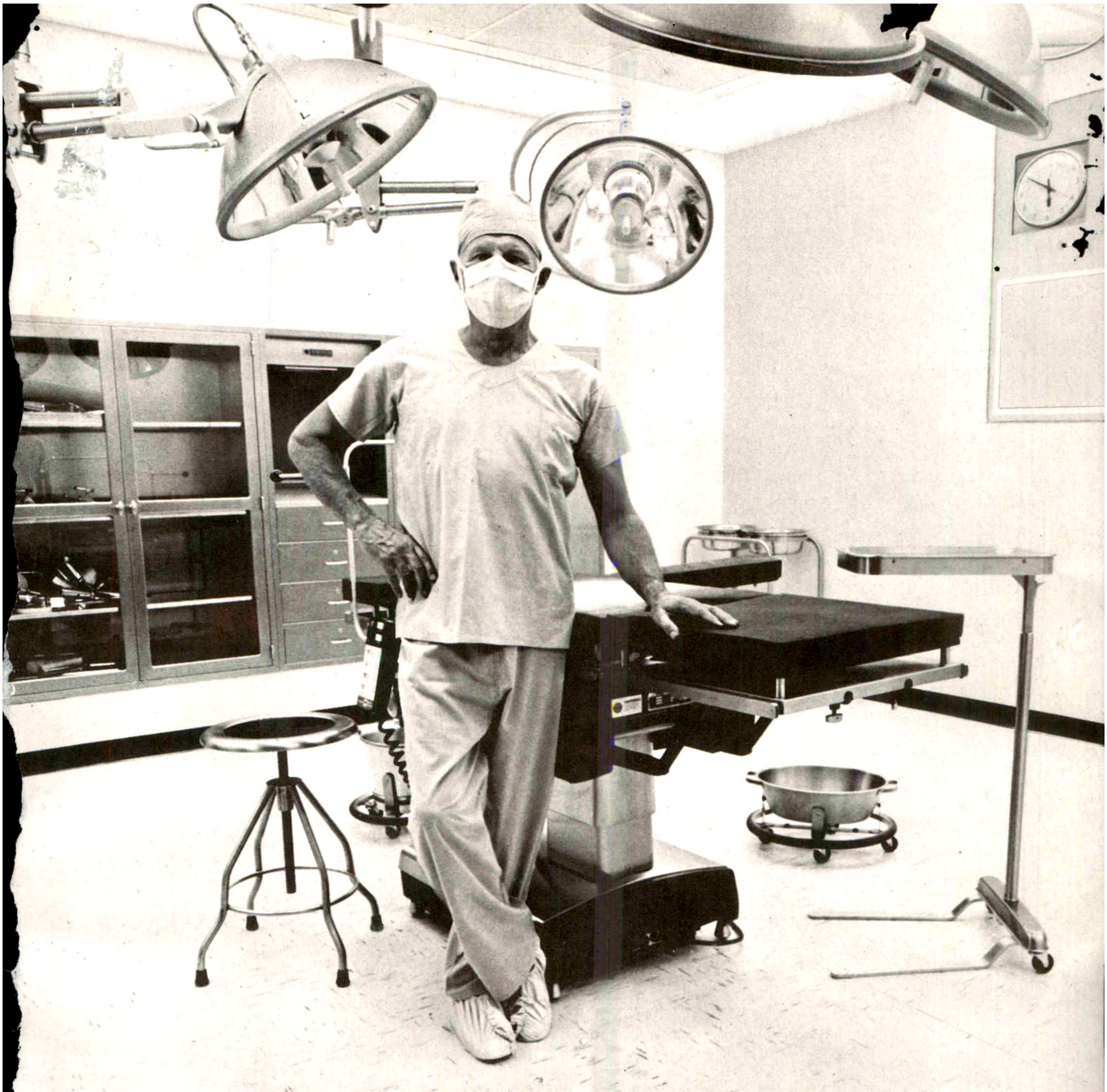
We figured two pictures were worth six words:



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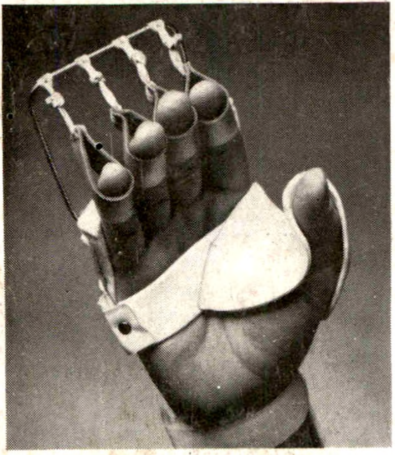

Wherever it hurts,
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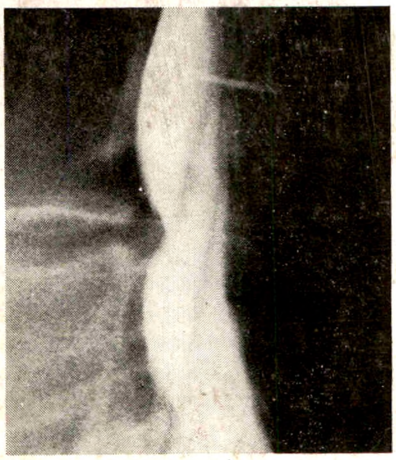
HERE Herniated intervertebral disc



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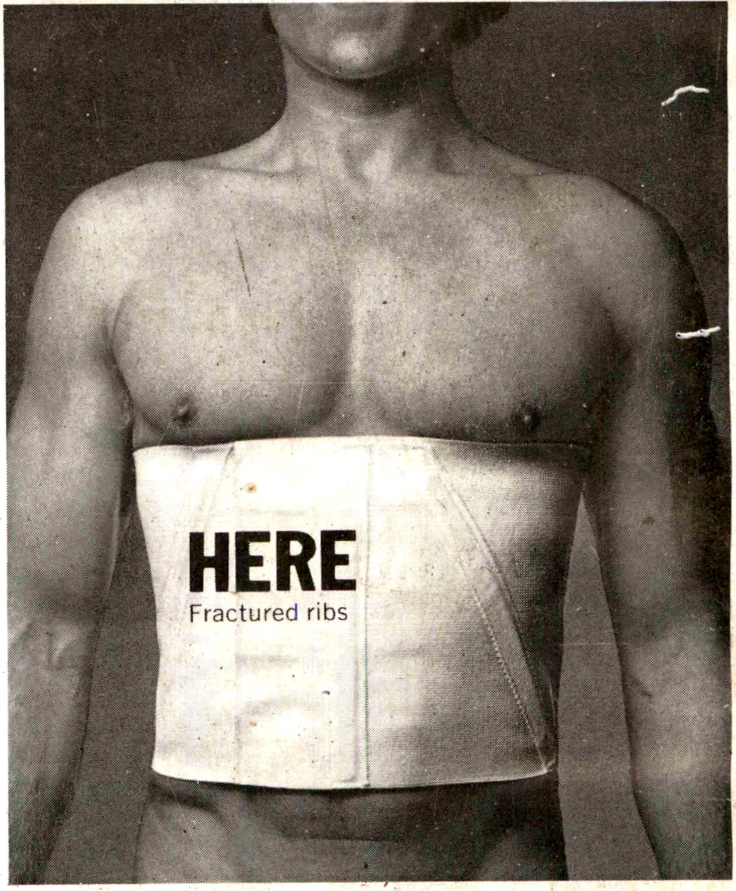

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